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Revolutionizing regenerative rehabilitation: 3D printing for musculoskeletal regeneration

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Abstract

Musculoskeletal disorders, such as bone fractures, osteoarthritis, meniscus injuries, muscle diseases, and tendon injuries, are common disorders among individuals in need of rehabilitation. Trauma, sports-related injuries, and degeneration mainly cause these disorders. Regenerative rehabilitation medicine aims to enhance the regenerative capacity of musculoskeletal tissues and optimize functional recovery through the combination of regenerative medicine and rehabilitation medicine treatments. However, these treatments are insufficient for the complete restoration of damaged tissue structures. Three-dimensional (3D) printing technology, referred to as the additive manufacturing (AM) technique, can accelerate the rehabilitation process for musculoskeletal diseases, especially for developing regenerative rehabilitation and engineering rehabilitation. Recently, an increasing number of studies reported on the basic and clinical applications of 3D printing in assisting with the treatment of musculoskeletal disorders. Therefore, this review summarizes how 3D printing technologies are changing treatment and assessment methods, as well as improving therapeutic outcomes in regenerative rehabilitation for musculoskeletal diseases. Finally, this review discusses the current status of the clinical translation for 3D printing.

***Keywords*:** 3D printing; Regenerative rehabilitation; Musculoskeletal disorder; Medical devices; Tissue engineering

1. Introduction

Musculoskeletal disorders are complex and common, comprising more than 150 different disease conditions. They are characterized by impairments in the muscles, bones, cartilage, joints, and connective tissues, which can lead to temporary or lifelong limitations in functioning and participation.[1,2] Generally, the symptoms are pain (often persistent), loss of function, and limitations in mobility and dexterity, which reduce the individual's ability to work and participate in society.[1] Moreover, the global burden of musculoskeletal diseases is increasing. A recent analysis of the Global Burden of Disease

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(GBD) reported that approximately 1.71 billion people globally live with musculoskeletal disorders, including bone fractures, osteoarthritis (OA), and other injuries.[3] Furthermore, musculoskeletal conditions are also the highest contributors to the global need for rehabilitation.[3] The current treatments of rehabilitation for these diseases include patient education, psychological interventions, physical therapy, exercise, use of assistive devices, and novel regenerative treatments, aiming to relieve symptoms, promote structural recovery, and improve function.[4–6]

Regenerative rehabilitation, first proposed by Ambrosio and Russell in 2010, "fuses" the characteristics of regenerative medicine and rehabilitation sciences.[7] The concept was further developed in 2018.[8] Regenerative rehabilitation integrates protocols, principles, and technologies of regenerative medicine and rehabilitation medicine. According to the International Classification of Functioning (ICF) model, rehabilitation focuses on the body's structure and function, activity, participation, and the relation between health conditions and contextual factors. From the perspective of the ICF model, regenerative therapy may accelerate tissue regeneration, repair, and functional reconstruction, ultimately improving the quality of life. With advances in tissue engineering and stem cell biology, regenerative rehabilitation can address broader challenges in biological sciences and healthcare.

Three-dimensional (3D) printing technology, referred to as an additive manufacturing (AM) technique, enables the fabrication of 3D constructs by the deposition of materials using computer-aided design and manufacturing techniques. Among them, 3D bioprinting (i.e., adding biomaterials to the inks) is the most popular branch of 3D printing. The field of rehabilitation has demonstrated advances when combined with engineering and organ regeneration. 3D printing technology involves precise fabrication from digital models that are built from individual data, offering tailored solutions that can significantly improve patient outcomes.[9] By precisely replicating the intricate structures of bones and tissues, 3D printing facilitates the development of individual-specific medical interventions. It has more incomparable advantages than other material-preparing methods, including the ability to fabricate complex products with a fast speed, high precision, high printing fidelity, controllable conditions, and cost-effectiveness.[10–12] Furthermore, it also can address the challenges associated with commercialization, stemming from insufficiency of standardization and industrialization in the preparation process.[13] Therefore, 3D printing technology has value in further research and applications in the field of regenerative rehabilitation for musculoskeletal disorders.

In this review, we introduce some standard material preparing methods and printing inks of 3D printing fabrication. We then discuss how 3D printing technologies are changing treatment and assessment methods, as well as improving therapeutic outcomes in regenerative rehabilitation for musculoskeletal diseases (Figure 1). Finally, this review assesses the current status of clinical translation for 3D printing.

2. Common 3D printing technologies for musculoskeletal regenerative rehabilitation

Generally, the core components of 3D printing technology are the printing equipment and printing inks. Herein, we summarize seven typical types of preparation methods for 3D fabrication and common printing inks.

2.1. Preparation methods of 3D printing technologies

3D printing technology, also known as rapid prototyping, is experiencing unprecedented growth and has become a versatile and advantageous platform for manufacturing various products in the medical field. The primary factors limiting its development are the printing materials and processes. After years of progress, 3D-printed biomaterials are now widely used in clinical medical practice. We summarize the key features of five major printing technologies, including inkjet printing (IP), stereolithography (SLA), extrusion-based printing, fused deposition modeling (FDM), and selective laser sintering (SLS), in the musculoskeletal repair field (Table 1).

In recent years, IP technology has gained popularity in various fields, such as drug delivery, tissue engineering, and disease modeling, due to its low cost, high efficiency, and precision. This technique allows for high-precision positioning of materials and cells[14] and single-cell printing[15] to create complex heterogeneous biomimetic structures. SLA can be subdivided into digital light processing (DLP), liquid crystal display, continuous liquid interface production, multi-jet printing, two-photon polymerization, and holographic 3D printing, based on the principles of pattern formation and printing technology.[16] Among these, DLP-3D printing is widely used in drug delivery, cell therapy, and tissue repair due to its high precision, achieving printing precision in the range of a few to tens of micrometers.[17] Extrusion-based printing is highly compatible with various rheological properties of materials and typically exhibits excellent mechanical performance and biocompatibility at room temperature. Extrusion-based printing can be used to manufacture a variety of products, such as medical devices, models, and biological scaffolds, but the filament formation process is

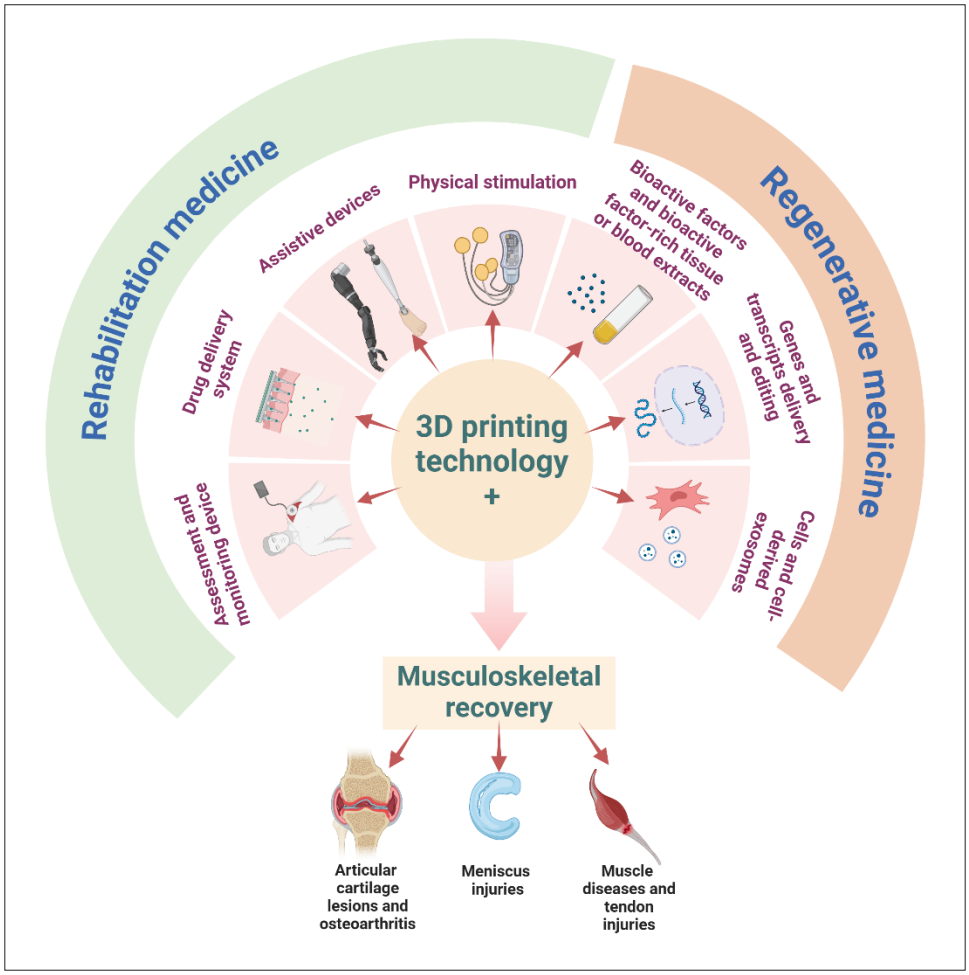

Figure 1. Schematic illustrations of 3D printing-based regenerative rehabilitation strategies. Created using BioRender (https://www.biorender.com/).

Table 1. Comparison of different 3D printing methods in the medical field.

Properties	Materials	Printing process	Resolution (μm)	Speed	Cell viability
Inkjet	Thermoplastic polymer	Serial (drop-by-drop)	50	Medium (mm/s)	> 85%
Light-based	Photosensitive polymer	Continuous plane (layer-by-layer)	1–6	Fast (mm^3/s)	85–95%
Extrusion	Thermoplastic polymer	Serial (line-by-line)	50	Slow (μm/s)	40–80%
FDM	Metals and alloys powder, ceramic, and polymer	Serial (line-by-line)	80	Slow (μm/s)	-
SLS	Metals and alloys powder, ceramic, and polymer	Serial (drop-by-drop)	80	Slow (μm/s)	-

Abbreviations: FDM, fused deposition modeling; SLS, selective laser sintering.

sensitive to temperature changes.[18] FDM enables flexible and complex designs, usually used in osteochondral tissue scaffolds and drug delivery systems.[19] The main drawbacks are the high temperatures required during printing, making it challenging to use materials and biologically active substances that are not resistant to high temperatures. SLS offers high precision, efficiency, and a wide range of material applicability, gaining increasing attention and application.[20] It can produce large quantities of products in a short time. Compared to other 3D printing technologies, it allows for mass production and rapid batch production of complex parts.[21] Each technology presents unique advantages and challenges essential for their application in biomedical fields.

2.2. Printing inks

The fundamental properties of a 3D-printed product can be determined by the material type and the assembly process. Common materials used for 3D printing include metallic materials (such as titanium alloys), inorganic materials (such as bioactive ceramics), organic materials (synthetic and natural polymer materials), and composite materials. In musculoskeletal applications, the common characteristics of materials used in 3D printing mainly include the following aspects:

(i) Printability: a crucial characteristic of these materials is their printability, which includes considerations of viscosity, flow properties, and the ability to maintain structural integrity during the printing process;

(ii) Biocompatibility: most materials, whether natural polymers, synthetic polymers, metals, or bioactive ceramics, must possess good biocompatibility to minimize adverse reactions when used *in vivo*;

(iii) Biodegradability: many materials (such as polylactic acid, polyesters, and natural polymers) demonstrate favorable biodegradability, allowing them to gradually break down within the body and reduce the risks associated with long-term implants;

(iv) Physical and mechanical properties: these materials are often engineered to exhibit specific mechanical strength and elasticity, dealing with different stress and tensile properties of tissues to support tissue regeneration and replacement;

(v) Modifiability: numerous polymers can be chemically modified to adjust their physical and chemical properties, such as altering crosslinking density or incorporating additional components to meet specific application needs;

(vi) Applicability in musculoskeletal regenerative rehabilitation: materials should have effects on the restoration of function and structure in damaged or diseased tissues.

2.2.1. 3D-printed materials for implants and scaffolds

Implants and scaffolds play a crucial role in the structural and functional reconstruction of the musculoskeletal system. They are often designed to exhibit bioactivity that promotes cell proliferation and differentiation and offers specific mechanical properties. They can provide mechanical support, fill defects in damaged areas, and serve as biodegradable scaffolds that facilitate tissue regeneration. 3D printing technology has significantly enhanced the development of personalized implants and scaffolds. This technique is characterized by its ability to support customized designs, ensure high reproducibility, maintain low production costs, and enable rapid prototyping. Additionally, it could fabricate scaffolds at micro and nano scales, thereby closely mimicking the natural structure and microenvironment of native tissues. Here, we introduce some commonly used materials in the fabrication of 3D-printed implants and scaffolds.

(i) Natural polymers: Natural polymers, extracted from natural materials, are compounds with low antigenicity, excellent biocompatibility, and biodegradability.[22] However, they have poor mechanical properties. Currently, commonly used natural polymers in 3D printing include collagen, gelatin, alginate, cellulose, chitosan, hyaluronic acid (HA), and decellularized extracellular matrix (dECM). While they have good biocompatibility and biodegradability, each material presents unique advantages and challenges (Table 2).

(ii) Synthetic polymers: Polyvinyl alcohol (PVA) is a water-soluble synthetic polymer known for its excellent biocompatibility, chemical stability, water absorption, non-toxicity, thermal stability, adjustable mechanical properties, and printability, making it a popular bioink in 3D printing.[23] Moreover, PVA exhibits strong hydrophilicity and hydrogen bonding properties due to its hydroxyl groups, forming gels with high physical stability. PVA hydrogels formed through crosslinking have various biomedical applications ranging from bone and cartilage regeneration to flexible sensors.[24–26] Polylactic acid (PLA), produced by ring-opening polymerization (ROP) of lactic acid, is one of the most consumed bioplastics globally. As a temporary extracellular matrix (ECM), PLA has good biodegradability, biocompatibility, and high ductility. However, pure PLA polymer has low mechanical strength. Thus, preparing PLA composites is needed to obtain better mechanical properties.[27] PLA is primarily used to manufacture degradable bone and cartilage tissue scaffolds. Polycaprolactone (PCL), a semi-crystalline polymer form of ε-caprolactone synthesized through ROP, is utilized in bone tissue engineering due to its biodegradability, non-toxicity, slow degradability, and high mechanical properties.[28] However, due to its poor hydrophilicity and low bioactivity, PCL used for tissue engineering scaffolds requires further combination with bioactive materials, such as tricalcium phosphate (TCP), hydroxyapatite (HA), Bio-Oss, or decellularized bone matrix to expand its application range.[29] Polyethylene glycol (PEG), a water-soluble polymer formed by polymerizing ethylene glycol, exhibits excellent biocompatibility and hydrophilicity. The stability

Table 2. The advantages and disadvantages of various natural polymers.

Type	Advantages	Disadvantages
Collagen	Excellent biocompatibility; low immunogenicity; abundant in the ECM	Limited mechanical strength
Gelatin and GelMA	Photopolymerizable to form hydrogels; controllable stiffness and porosity by adjusting parameters (e.g., hydrogel concentration, functionalization degree, and curing time); excellent biocompatibility and biodegradability	May require modification for improved stability
Alginate	Forms hydrogels under mild conditions; promotes bone healing and cartilage regeneration by regulating cell viability, osteogenic inductivity, and chondrogenic differentiation of MSCs; good biocompatibility, biodegradability, and non-antigenicity	May lack cell adhesion sites
Cellulose	Excellent mechanical properties; suitable for weight-bearing implants; degradable	Poor solubility (requires modification)
Chitosan	Mimics glycosaminoglycans in the ECM	Insufficient mechanical strength; unsatisfactory degradation rate
HA and MeHA	Non-toxic and non-immunogenic; good biocompatibility and biodegradability; improved physical properties (MeHA); extensively used in bone and cartilage tissue engineering	May require chemical modification for enhanced stability
dECM	Maintains various functional components that can support cell survival, growth, migration, and differentiation; mimics the native ECM structure to provide a more biomimetic environment for cells; good biocompatibility and low immunogenicity	Limited mechanical properties; potential for disease transmission; time-consuming and expensive production process; challenges in obtaining large quantities of tissue-specific dECM

Abbreviations: dECM, decellularized extracellular matrix; ECM, extracellular matrix; GelMA, methacrylate-based gelatin; HA, hyaluronic acid; MeHA, methacrylated hyaluronic acid; MSCs, mesenchymal stem cells.

and degradation rate of PEG hydrogels notably affects its applications. The ester bonding caused by acrylation slows the degradation rate of PEG. The biocompatibility and low immunogenicity of the acrylate-derivatives of PEG hydrogel make it a good choice for in-body applications.[30]

(iii) Metals: 3D-printed metals are primarily used in orthopedics for implants, as well as in soft robotics, sensor technology, and *in vitro* medical devices.[31,32] The type of metal material chosen depends on specific clinical needs. Most orthopedic implants are made of inert metals (cobalt–chromium alloys), some need to bond with host tissue (titanium alloys), and some require tissue growth to eventually replace the implant (magnesium alloys).[33] Current metal implants primarily use cobalt–chromium alloys and titanium alloys. Implantable metals must possess biocompatibility, corrosion resistance, high specific strength, high fatigue strength, high impact toughness, and low toxicity. One key issue with implants is stress shielding, which leads to bone loss due to the implant's inhibition of pressure on the bone. Stress shielding can be addressed by using materials with stiffness similar to cortical bone (e.g., magnesium) or by designing implants with porosity to reduce stiffness.[34]

(iv) Bioactive ceramics: Bioactive ceramics are a class of ceramic materials used for specific biological or physiological functions. They can be classified into three major categories: bioinert ceramics (alumina and zirconia), bioactive ceramics (bioactive glass and HA), and biodegradable ceramics (TCP). Each bioactive ceramic has its unique characteristics, such as the high hardness of alumina ceramics, the toughness of zirconia ceramics, and the chemical composition of HA, closely resembling the inorganic part of human bone. However, a common disadvantage of ceramics is their brittleness, leading to high costs and difficulty in forming complex shapes with traditional processing techniques.[35] 3D printing, an emerging manufacturing technology, offers advantages such as rapid prototyping, personalized production, and the formation of complex structures. The combination of 3D printing technology and bioactive ceramics meets the needs requirements for individualized treatment in the biomedical field.[36]

2.2.2. 3D-printed materials for rehabilitation assistive devices

3D-printed rehabilitation assistive devices mainly include prosthetics and orthotics, with the advantages of cost-effectiveness, lightweight, comfort, and breathability compared to traditional plaster or plastic devices. The

commonly used materials can be categorized into rigid and flexible materials. PLA and acrylonitrile butadiene styrene are the most widely used thermoplastic materials, commonly employed in FDM and SLS printing techniques.[37] Among flexible materials, thermoplastic polyurethane (TPU) is commonly used, often in FDM, SLS, and multi-jet fusion (MJF) printing techniques.[38] Additionally, composite materials have significantly enhanced stiffness, weight, and patient comfort. Recently, 3D-printed rehabilitation aids have evolved towards more complex and intelligent designs. For instance, Buchner et al. designed a tendon-driven hand capable of performing intricate actions such as grasping.[39] Moreover, 3D-printed braces can be integrated with monitoring systems to facilitate biomechanical analysis of joints, postoperative recovery monitoring, functional exercise assistance, and adjustments to rehabilitation programs.[40] Therefore, it is necessary to develop materials with higher strength and toughness and composite materials that support collaborative printing techniques, which enables the production of intricate, high-resolution, and precise devices while ensuring patient comfort and safety. Furthermore, it is essential to develop smart materials capable of responding to environmental changes, such as temperature, humidity, or force. These materials could adaptively adjust their properties during the rehabilitation process, providing personalized feedback and support tailored to the individual needs of patients. This integration of advanced materials and intelligent functionalities holds the potential to significantly enhance the efficacy and user experience of 3D-printed rehabilitation aids.

3. Impact of 3D printing technology on musculoskeletal regenerative rehabilitation methods

Functional recovery is a primary concern for patients with musculoskeletal system injury. Functional rehabilitation refers to the restoration of function in patients through rehabilitation strategies, which is critical for regaining physical function and enhancing quality of life. Physical factors, including light, sound, heat, force, and electrical and magnetic fields, play very important roles in rehabilitation medicine, aiming to minimize inflammation, relieve pain and swelling, and restore the function of damaged or aged tissues and organs. The beneficial effects of physical stimulation, such as mechanical, electrical, and magnetic stimuli, and therapeutic ultrasound, on cell viability and biological efficacy of different cells, including meniscal cells, fibroblasts, osteoblasts, chondrocytes, and mesenchymal stem cell-derived exosomes, have been investigated in previous studies.[41–44] In addition, physical factors can also regulate immune cell function and angiogenesis, as well as reducing inflammation and oxidative stress, thereby forming a microenvironment conducive to tissue repair.[45,46] The combination of physical stimulation and 3D printing technology enhances tissue repair.

The effective implementation of functional rehabilitation requires the coordination of rehabilitation assistive devices, which are defined as techniques designed to compensate for and enhance function.[47] With the increasing demand for customization, the 3D printed approach has found widespread application in the fabrication of personalized rehabilitation assistive devices tailored to the unique conditions of individual patients. 3D-printed assistive devices, including prostheses and orthoses, are well-fitting to patients' bodies and streamline procedures of recapitulation of patient-specific color, texture, stiffness, and shape. Moreover, they are more favorable in improving functional outcomes, such as reducing pain, improving comfort, preventing joint stiffness, and regaining range of motion.[48–51] For instance, a printed upper limb prosthesis for a child with traumatic amputation of the right wrist met the child's daily living needs, costing less than $20 and requiring less than 8 h for fabrication.[52] The fabrication of 3D-printed rehabilitation assistive devices has advantages in terms of time, cost-effectiveness, and environment-friendliness.[51–54] Therefore, 3D-printed rehabilitation assistive devices are an affordable, satisfying, and customizable alternative for patients with a variety of orthopedic conditions, including amputations, fractures, sprains, ligament tears, and tendinopathies.

Pharmacological interventions, such as corticosteroids and nonsteroidal anti-inflammatory drugs, are commonly applied to reduce inflammation and relieve pain, thus accelerating the repair of damaged tissues and reducing the time required for return to sports. However, systemic administration is usually associated with significant known risks.[55] Therefore, 3D-printed technology facilitates the development of precisely controlled drug delivery. For example, Majrashi et al. fabricated 3D-printed scaffolds capable of sustainably releasing dexamethasone locally, with dual capacities of anti-inflammation and pro-osteogenic differentiation. This highlights the potential of 3D printing technologies in developing precisely controlled drug delivery systems and reducing systemic side effects.[56]

The strategies of regenerative medicine to repair damaged and aged tissues and organs today rely on three types of biological components:

(i) Bioactive factors such as bioactive molecules (E7, R5, and Apt19s) and growth factors (transforming growth factor-beta [TGF-β] and platelet-derived growth factor-BB), and bioactive factor-rich tissue or blood extracts (platelet-rich plasma [PRP], platelet-

rich fibrin, bone marrow aspirate concentrate, autologous fat grafting, and stromal vascular fraction);

(ii) Genes and transcripts delivery and editing, in which tissue function is enhanced at the genetic level;

(iii) Cells and cell-derived exosomes, in which mesenchymal stem cells (MSCs), human umbilical vein endothelial cells, myoblasts, osteoblasts, and chondrocytes are commonly used in the treatment of musculoskeletal diseases.

In addition, tissue engineering and biomaterials combine principles from engineering, biology, and materials science to develop biological substitutes aimed at restoring, maintaining, or improving tissue function. They involve the use of biological components and biomaterial scaffolds to create functional tissue constructs that can be implanted or injected into the body to repair or replace diseased tissues. The integration of 3D printing technologies with tissue engineering and biomaterials has opened up new possibilities for creating more complex, functional, and personalized tissue constructs and implants, ultimately advancing the field of regenerative medicine and improving patient outcomes.

Regenerative rehabilitation, the fusion of regenerative and rehabilitation medicine, was first proposed by Ambrosio and Russell in 2010.[7] The concept was further elaborated by Rando and Ambrosio in 2018.[8] This emerging field aims to optimize the restoration of function through the integration of principles, protocols, and approaches of two similar fields. A recent network meta-analysis of 80 randomized controlled trials (RCTs) revealed that, compared to physical therapy alone or intra-articular injection of PRP or MSCs alone, the combination of physical therapy and regenerative therapy was more efficacious in reducing pain and enhancing walking capability for patients with knee OA.[57] A phase I/II clinical trial for patients with knee OA indicated that 1 year after implantation of a composite of culture-expanded allogeneic human umbilical cord blood-derived mesenchymal stem cells and HA (hUCB-MSCs-HA) hydrogel and postoperative exercises, regenerated cartilage with a smooth surface was observed at the defect sites. Besides, no significant adverse events were observed after 7 years of follow-up.[58] However, evidence from clinical studies is still limited for the efficacy and safety of cell transplantation and PRP injections. The impact of individual patient differences on efficacy cannot be ignored. Significant progress has been achieved in regenerative rehabilitation medicine through the advancements of 3D printing technology. The development of 3D printing technology has promoted the personalization, precision, and complexity of regenerative rehabilitation technology, resulting in more efficient tissue repair. Figure 2 summarizes the complete workflow for the 3D printing-based musculoskeletal regenerative rehabilitation process.

4. 3D-printed solutions in tissue regeneration for musculoskeletal disorders

4.1. Articular cartilage

Articular cartilage lesions commonly result from trauma induced by an external force or age-related degeneration.[59] Articular cartilage is a highly organized tissue with multilayer structures, including the hyaline cartilage layer and the underlying calcified cartilage layer, which provides a smooth joint surface and exhibits high elasticity, high toughness, high stiffness, and fast recovery.[13] Therefore, it can withstand a load of up to 100 MPa, can be less prone to fatigue, and can rapidly recover its deformation after unloading.[60] Progressive loss of articular cartilage induces joint inflammation, cartilage ECM remodeling, gradual tissue deterioration, and bone remodeling, ultimately resulting in the development of OA.[22,61–63] However, its ability of intrinsic repairment is poor due to low proliferative capacity and a lack of neurovascular components.[22] Besides, traditional therapies cannot fully restore the multilayered structure and complex interaction of cartilage. Thus, 3D printing-based cartilage tissue engineering is a potential choice.

3D-printed implants can facilitate tissue reconstruction due to their similar structure and biological function to normal cartilage. In addition, they can promote the growth and proliferation of chondrocytes by introducing beneficial cells, growth factors, and bioactive molecules. Selecting suitable materials is significant to the ideal function. Natural polymer materials have been widely explored as bioinks due to low antigenicity, biocompatibility, and degradability.[60] Li et al. fabricated a 3D-printed microenvironment-specific biomimetic hydrogel scaffold using GelMA, dopamine-grafted HA (HA-DA), and oxidized HA with the addition of the dECM derived from cartilage and bone encapsulated exosomes.[64] At 12 weeks after implantation in a rat model with osteochondral defect, the scaffold promoted the formation of hyaline cartilage, resembling the structure of normal tissue (Figure 3A). Moreover, 3D-printed PRP-laden GelMA hydrogel constructs remarkably facilitate superior cartilage and subchondral bone repair by promoting the migration and osteogenic and chondrogenic differentiation of bone marrow MSCs (BMSCs). Additionally, these constructs participate in the regulation of immune responses and mediate the transition of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory and pro-regenerative M2 phenotype.[65] The 3D-printed scaffold could mimic the

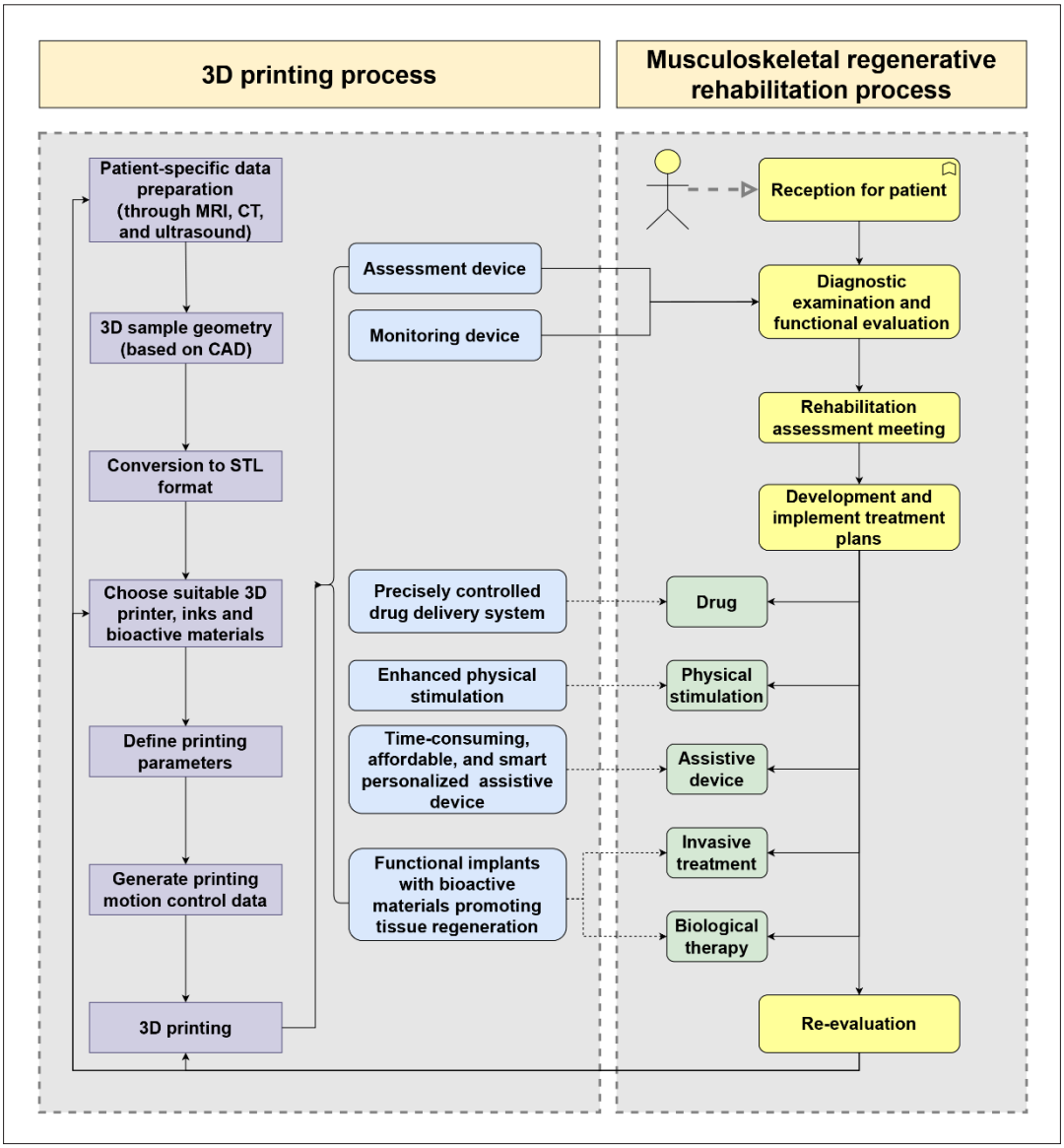

Figure 2. The 3D printing-based musculoskeletal regenerative rehabilitation process. Abbreviations: CAD, computer-aided design; CT, computed tomography; MRI, magnetic resonance imaging.

complex layers of normal articular cartilage. For example, Zhang et al. fabricated a multilayered nanohydroxyapatite (nHA)/hydrogel scaffold with a similar structure to that of osteochondral tissue, which possesses an increasing stiffness gradient from the cartilaginous layer to the subchondral bone layer. The scaffold exhibited remarkable mechanical properties, appropriate degradability, and high structural integrity for long periods of cell culture.[66]

Mechanical stimulation is a decisive factor for cartilage tissue formation. For example, a 12% compressive strain stimulated the generation of hyaline-like cartilage ECM, while a 24% compressive strain tended to produce fibrocartilage-like ECM.[67] However, there is no rigorous standard to identify the optimal parameters including type, intensity, volume, frequency, duration, timing, and progression of application. It is also unclear whether a traditional rehabilitation regimen is appropriate for patients receiving cartilage scaffold implantations. Inappropriate mechanical stimulation can cause substantial damage to the structure. A study indicated that mechanical compression for 5 days (3 h/day) could damage the hydrogel constructs, especially at 12% and 24% compressive strain conditions.[67] Hydrogel scaffolds with better mechanical properties may be able to withstand higher mechanical forces, effectively

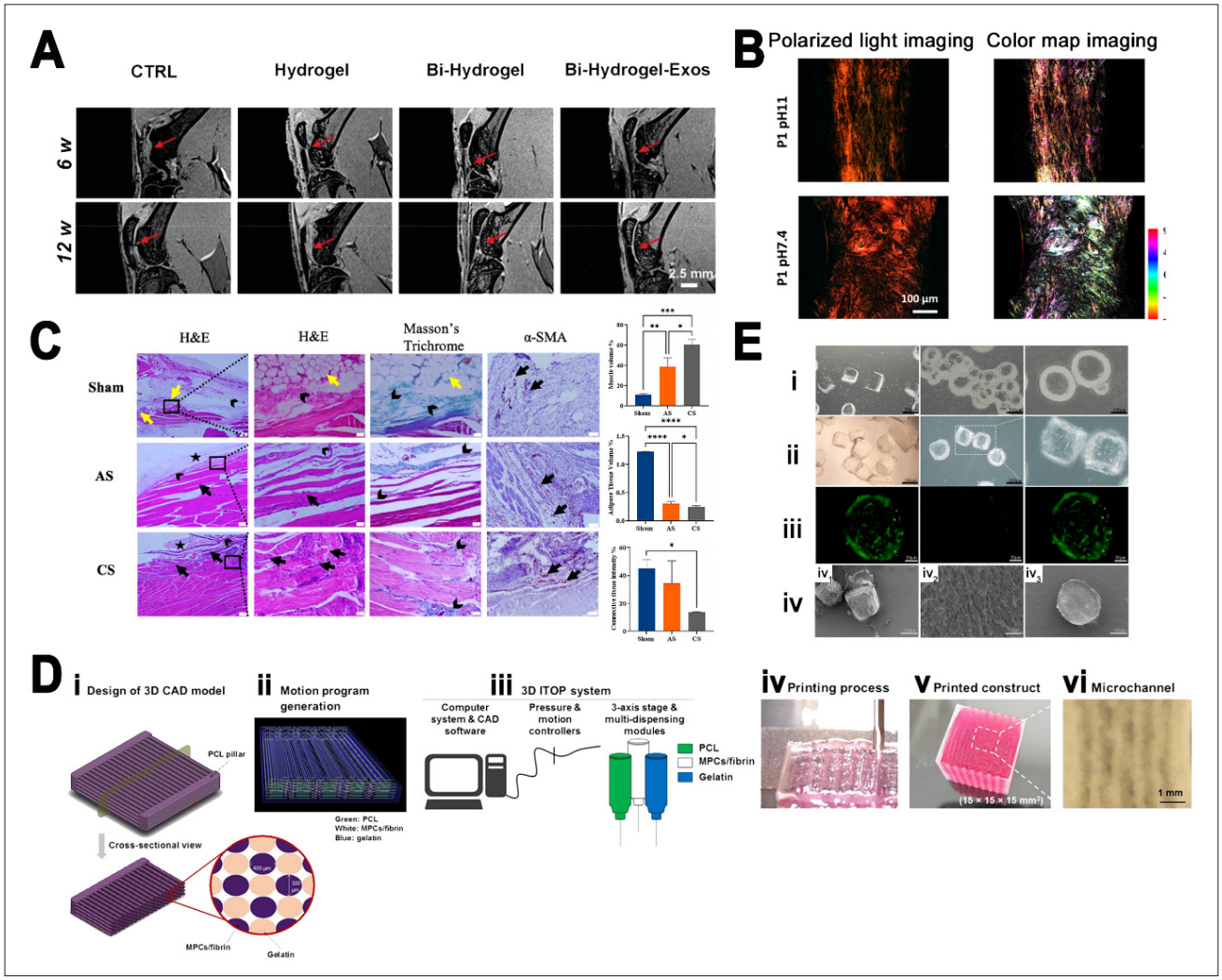

Figure 3. 3D printing-based treatment of musculoskeletal diseases. (A) MRI outcomes indicate that 3D-printed tissue-specific microenvironment biomimetic scaffolds promoted cartilage repair. Adapted with permission from Li et al.[64] Copyright © 2023 The Authors. Reprinted under the terms of the CC-BY license. (B) The direction of collagen fibers in printed ECM filaments with pH 11 compared to pH of 7.4. Adapted from Wang et al.[81] (C) Histopathological results of the defect region after four weeks implantation for the empty, AS, and CS groups in a rat tibialis anterior defect model. Adapted with permission from Gokyer et al.[101] Copyright © 2021 American Chemical Society. (D) 3D-printed skeletal muscle constructs: (D, i) design of the 3D model in CAD; (D, ii) motion program generation of the bioprinted muscle construct; (D, iii) schematic of the bioprinting process using the ITOP system; (D, iv) bioprinting process; (D, v) the bioprinted skeletal muscle constructs composed of multilayered myofiber bundles were fabricated up to 15 × 15 × 15 mm^3 in dimension; (D, vi) microchannels in the constructs created after the removal of the sacrificial patterns to maintain the viability of printed cells. Adapted with permission from Kim et al.[104] Copyright © 2018 The Author(s). Reprinted under the terms of the CC-BY license. (E) 3D printed GM co-cultured with TDSCs for tendon repair: (E, i) GelMA GM under an optical microscope; (E, ii) co-culture of TDSCs and GM; (E, iii) immunofluorescence staining of living (green) and dead (red) cells on GM; (E, iv_1) GM under SEM (×30000); (E, iv_2) surface morphology of GM under SEM (×30,000); (E, iv_3) Cross-section of GM under SEM (×30,000). Adapted from Li et al.[109] Abbreviations: AS, acellular scaffold; CAD, computer-aided design; CS, cell-laden scaffold; CTRL, blank control; ECM, extracellular matrix; GelMA, gelatin methacryloyl; GM, microparticles; ITOP, integrated tissue-organ printer; MPCs, muscle progenitor cells; MRI, magnetic resonance imaging; PCL, poly(ε-caprolactone); SEM, scanning electron microscope; TDSCs, tendon-derived stem cells.

enhancing their performance by adjusting manufacturing process parameters. Regulating the printing parameters (pressure,[68] moving speed,[68] and concentration of printing inks[69,70]) could change the mechanical properties of scaffolds. In addition, the introduction of silk fibroin and inorganic materials in the fabrication process is also a strategy to achieve desirable mechanical properties.[71,72] It should be noted that clinical trials are lacking to verify whether tissue-engineered cartilage can withstand long-term loads experienced by humans. However, this goal may not be necessary, as the majority of tissue-engineered cartilage constructs are typically designed to be biodegradable.

The ultimate objective is to enhance endogenous repair, rather than to depend on xenogenic scaffolds for structural support. In a phase I/II clinical trial, MRI scans of five participants with OA who received implantation of a composite of hUCB-MSCs and HA hydrogel, combined with postoperative rehabilitation (including muscle strength and joint mobility exercises, and non-weight-bearing ambulation), demonstrated regenerated cartilage comparable to that of healthy individuals.[58]

Physical factors are important for regenerative rehabilitation. Physical stimuli acting on mechanochemical transduction pathways may potentially reduce reliance on the mechanical properties of tissue-engineered cartilage. For example, low-intensity pulsed ultrasound (LIPUS) can modulate the integrin-FAK-PI3K/Akt pathway in OA chondrocytes, enhancing ECM production and reducing metalloproteinase levels.[73] Physical stimuli have been proven to promote cartilage regeneration and differentiation. 3D-printed flexible, conductive, and biodegradable scaffolds have the potential to control electrical stimulation in damaged cartilage areas.[74] Stimuli-responsive hydrogels (e.g., light, temperature, and magnetic) can be combined with physical therapies used in rehabilitation medicine (e.g., infrared light, magnetothermal therapy, and pulsed electromagnetic fields) to achieve precise treatment of damaged cartilage in patients. However, further development of bioinks suitable for clinical applications is necessary.

Rehabilitation medicine teams should collaborate with tissue engineering experts to develop regenerative rehabilitation strategies. This collaboration aims to optimize and enhance the repair performance of tissue-engineered cartilage in humans, thereby accelerating its clinical application.

4.2. Meniscus

The meniscus, a complex and crucial fibrocartilaginous tissue within the knee joint, assumes a semilunar wedge-shaped form that plays a pivotal role in ensuring the overall functionality of the joint.[75] Positioned between the femoral condyle and the tibial plateau, the meniscus undertakes the imperative functions of transferring and redistributing loads, providing cushioning, and absorbing shock, as well as joint lubrication and congruent stability.[76] Age-related degeneration and acute sports injuries are commonly acknowledged as two principal contributors to meniscal dysfunction.[77] Due to the inherent limited vascularity and suboptimal healing capacity of the meniscus,[78] the pursuit of desirable and sustained outcomes remains difficult. Meniscus injury and absence due to meniscectomy render the hyaline cartilage of the femur and tibia susceptible to excessive biomechanical forces, consequently accelerating the development of OA.[77,79,80] Given the unique anatomical structure and complex stress environment of the meniscus, meniscal regeneration remains to be a scientific and translational challenge. To this end, meniscal tissue engineering has emerged as a potential approach for treating meniscal defects.

Recently, appropriate biomimetic scaffolds have been constructed via 3D printing, imitating elaborate microstructure of the native meniscus with structural integrity and high-strength comprehensive mechanical properties. Wang et al. successfully used highly concentrated meniscus dECM inks at pH 11 to print artificial meniscus. These functional meniscal tissue equivalents had a compressive modulus comparable to that of a natural meniscus and could control the alignment of collagen fibrils (Figure 3B).[81] Characterized by a unique shape with high edges and a low center, the meniscus faces a complex stress environment, encompassing axial, hoop, and compressive mechanical stresses.[82] However, it is challenging to develop a meniscal replacement that recapitulates the anisotropic microarchitecture and modulus of the meniscus. To this end, Jian et al. developed a biomimetic meniscal scaffold using a multilayer strategy.[83] By employing a dual-nozzle and multi-temperature 3D bioprinting system, they integrated PCL with meniscal fibrocartilage chondrocyte-laden GelMA/meniscal ECM bioinks, achieving optimal biomimetic features in morphology and components. With a compression modulus of 12.63 MPa and a tensile modulus of 24.86 MPa in the radial direction, close to those of the human meniscus, this approach showcases promising advancements in creating functional meniscal replacements for potential applications in tissue engineering and regenerative medicine. However, the mechanical properties attained through this approach still exhibit a significant discrepancy when compared with the circumferential tensile modulus (78–120 MPa). To provide circumferential tensile supports, Zhang et al. 3D printed the radially and circumferentially oriented PCL fiber framework to imitate collagen fibers in the native meniscus.[84] Meanwhile, poly(N-acryloyl glycinamide) hydrogel was infused into the 3D-printed PCL framework, thus providing durable energy absorption and cushioning. The *in vivo* results demonstrated structural stability, efficient protection against cartilage wear, and an ameliorating effect on OA development. The 3D printing approach can handle complex requirements of mechanical properties of joints, presenting a fresh possibility for future meniscal regeneration strategies.

The meniscus exhibits a highly intricate microarchitecture characterized by the presence of diverse cellular types, ECM components, and organization in various regions, highlighting the heterogeneity of this

fibrocartilage.[76,85,86] The meniscal ECM comprises a densely woven and well-hydrated meshwork interlaced with circumferential collagen fibers and radial collagen fibers, interspersed with glycosaminoglycans (GAGs). Furthermore, the outer region, rich in fibroblast-like cells that exist within an ECM that mainly comprises type I collagen (Col I), confers resistance against tensile loads, while the inner region, rich in chondrocyte-like cells, which are embedded within an ECM that largely consists of type II collagen (Col II) and GAGs, contributes to resistance against compression. To promote anisotropic regeneration of meniscus-like tissue, Yan et al. developed a 3D-printed biomimetic meniscal scaffold loaded with intrinsic MSCs and growth factors, including TGF-β3 and connective tissue growth factor, known for their superior fibrochondrogenic capabilities.[87] The neomenisci exhibit an anisotropic matrix distribution, with the inner and middle zones abundant in Col II, aggrecan, and GAG, while the outer zone primarily contains Col I. Consequently, the anisotropic matrix distribution in the regenerated tissue enables shock absorption during knee joint motion, resembling the native menisci. In addition to matrix distribution, the distribution of cells in the meniscus is also anisotropic. Chae et al. printed a biomimetic meniscus construct using polyurethane (PU) and PCL polymers and cell-laden decellularized meniscal ECM (me-dECM) bioink.[88] The resulting neomeniscus displayed rounder chondrocyte-like cells and fewer fibroblast-like cells in the inner region of the neomeniscus at 8 weeks compared to 4 weeks, thus exhibiting favorable mechanical and biological properties similar to the native meniscus. Overall, 3D-printed scaffolds reconstruct anatomical structures and restore knee mobility and stability, making them promising options for regenerative meniscus repair.

Mechanical stimuli are significant for menisci to synthesize proteins and regulate cellular processes.[89] Ultrasound has been used to mechanically stimulate chondrocytes through integrin-mediated signaling pathways.[73,90] The combination of LIPUS and 3D hybrid scaffolds can promote chondrocyte migration, adhesion, proliferation, and viability, retain chondrocyte morphology, and increase the expression level of Col II and aggrecan.[91] Thus, mechanical stimuli through physical factors should be added to the 3D-printed tissue engineering to enhance tissue functions.

4.3. Muscle

Muscle diseases are conditions that affect the human muscular system, usually caused by injury, infection, aging, and hereditary factors, resulting in muscle wasting, loss of muscle mass, and decreased muscle strength.[92] Strength training and aerobic exercise programs are performed to improve muscle strength and muscle endurance.[93] Additionally, functional free muscle transfer procedures and the implementation of advanced orthotic bracing designs are adapted as therapeutic options for severe muscle diseases.[94] However, they fail to significantly improve functional outcomes and increase associated donor site morbidity.[95] In recent years, regenerative medicine and tissue engineering using 3D printing are emerging, aiming to more fully restore muscle form and function.

Volumetric muscle loss (VML) involves a severe loss of muscle tissue that transcends the inherent regenerative capabilities of skeletal muscles.[96] Traditionally, the gold standard for VML defect treatment is autologous muscle tissue implantation, yet these implants frequently exhibit poor efficacy and may lead to failure due to low regeneration efficiency stemming from the inadequate controllability of myofiber structural organization.[97] In response, tissue engineering structures employing synthetic or natural biomaterials tailored to artificial muscle tissues, coupled with live cells, have been developed to enhance muscle functions.[98] The bioprinting process provides controllable 3D spatial cell distribution in 3D frameworks with no effect on their activities.[99] In one example, Hwangbo et al. fabricated aligned muscle construct by using GelMA-based cell-laden structures, incorporating C2C12 or human adipose stem cells (hASCs), with an *in situ* UV crosslinking system for treating VML.[100] The study successfully developed GelMA structures with uniaxially aligned C2C12 cells, optimizing printing parameters to enhance cellular alignment and myotube heavy chain expression. *In vivo* experiments with hASC-laden muscle constructs demonstrated significant functional and volumetric restoration in VML-defective mice compared to conventionally crosslinked structures. Seyda et al. 3D printed biodegradable elastomeric TPU-based scaffolds seeded with autologous ASCs. After scaffold implantation in a rat tibialis anterior defect model, organized muscle regeneration significantly increased (Figure 3C).[101] The electrical activity and active force produced by the regenerated muscle were also increased, indicating that the scaffold enhanced the function of regenerative muscles.

The skeletal muscle is widely recognized for its high degree of vascularization, a crucial aspect for providing nutrients and oxygen and removing metabolic waste within the muscle tissue.[102] Despite its importance, the bioprinting of micro-vascularized skeletal muscle tissues presents ongoing challenges. Addressing this, Luo et al. employed the vertical 3D cryo-bioprinting technique to successfully fabricate the muscle-microvascular unit.[103] This innovative approach utilized C2C12 myoblasts and human umbilical vein endothelial cells, demonstrating a significant advancement in the development of micro-

vascularized skeletal muscle constructs. In another study, Kim et al. employed the integrated tissue-organ printer (ITOP) system to create a 10 × 7 × 3 mm^3 skeletal muscle construct with human muscle progenitor cells in a fibrin bioink with gelatin and PCL deposition (Figure 3D).[104] The construct, transplanted into the tibialis anterior (TA) muscle defect rat model, displayed enhanced tetanic force and TA muscle weight, with 82% muscle force restoration compared to normal TA muscle after 8 weeks. Moreover, it was well integrated with host vascular and neural networks. Thus, 3D bioprinting improves the accuracy and survival rate of muscle tissue constructs.

4.4. Tendon

Tendons are load-bearing structures that transmit forces from muscle to bone.[105] It is a type of connective tissue with minimal cellular presence and abundant collagen fibers organized in parallel alignment.[106] Tendon tears often occur due to strenuous exercise and age-related degeneration, accounting for over 30% of all musculoskeletal consultations.[107] Present therapeutic alternatives are limited, predominantly involving symptomatic interventions and surgeries. While surgical interventions may provide temporary relief for certain symptoms, the long-term effects, such as tendon adhesion, inferior mechanical properties, and the risk of re-injury, are unsatisfactory.[108] Owing to unsatisfactory outcomes of surgeries, engineered biomimetic tendon grafts that emulate the intrinsic properties of native tissues have been explored. Li et al. designed injectable GelMA microparticles (GM) laden with PRP and tendon-derived stem cells (TDSCs) to promote Achilles tendon regeneration and inhibit chronic inflammation by downregulating the PI3K-AKT pathway (Figure 3E).[109] In addition, Zhang et al. combined a small molecule culture system with 3D printing to create tendon grafts embedded with TSPCs, facilitating functional tendon repair and regeneration in both the ectopic and *in situ* tendon repair models.[106] Moreover, Kim et al. created a cell-laden construct for tendon tissue engineering, utilizing hASCs, and a dECM bioink derived from porcine tendon.[110] The resulting cell constructs exhibited controllable mechanical properties and significantly enhanced cellular activity. Notably, they showcased uniaxially aligned cell morphology and upregulated tendon gene expression, emphasizing the potential for advancing tendon tissue engineering.

3D printing is also applied to deal with the difficulties of repairing tendon–bone junctions. Rotator cuff tears, a common tendinopathy, resulting from acute trauma or chronic degenerative disorders, present challenges in restoration of the tendon–bone interface.[111,112] The native tendon-to-bone interface, comprising tendon, fibrocartilage, mineralized fibrocartilage, and bone, is intricate and challenging to restore owing to a lack of oxygen, growth factors, and other metabolically essential nutrients.[113] Current healing processes often lead to fibrovascular tissue formation instead of fibrocartilage regeneration, hindering biomechanical transduction, and causing dysfunction.[114] Consequently, the complex rotator cuff enthesis requires the exploration of biomimetic interfaces to improve surgical outcomes, offering potential alternatives and *ex vivo* living grafts. The evolving fields of tissue engineering and stem cell biology provide optimism for enhancing repaired tendon quality. For example, Cao *et al.* fabricated a biomimetic tendon-to-bone interface using a 3D-printed PCL–PCL/TCP–PCL/TCP multiphasic scaffold and a stratified cell-seeding method with GelMA.[115] Designed with three phases resembling the tendon, fibrocartilage, and bone, the scaffold facilitated the independent seeding of fibroblasts, BMSCs, and osteoblasts. This biomimetic approach offers potential applications in rotator cuff tendon-to-bone repair, serving as an alternative to biological fixation devices and providing an *ex vivo* living graft for damaged entheses.

In muscular tissue engineering, reconstructing the muscle–tendon unit (MTU) is a formidable challenge. The key part of MTU is the muscle–tendon junction, which transmits the mechanical forces of the muscle through the tendon to the skeletal system.[116] Luo et al. have developed an enabling vertical 3D cryo-bioprinting technique by combining extrusion bioprinting, directional freezing, and cryopreservation.[103] Applying this method to MTU fabrication using C2C12 myoblasts and NIH/3T3 fibroblasts, the resulting structures mimic the natural MTU. By strategically aligning cells and optimizing GelMA bioink formulations, this study advanced the precise control of bioprinting complex tissue structures.

5. Novel 3D-printed medical devices for musculoskeletal disorders

Medical devices play a crucial role in facilitating and augmenting regenerative and rehabilitative processes. A range of 3D-printed medical devices have been designed to support, monitor, assess, or enhance the delivery of regenerative treatments and rehabilitation interventions, contributing to the overall objective of improving patient outcomes.

Another challenge faced by researchers is the lack of sensors capable of non-invasively or implantably monitoring tissue responses to physical stimuli *in vivo*. 3D printing can be employed to manufacture assessment and monitoring devices to assess the progress of regenerative rehabilitation. Hou et al. developed a conductive ink

using the graphene nanoplate-carbon nanotube (GC) ink as the fusing agent (FA) for MJF printing to fabricate multilayered strain and humidity sensors, which can be used to monitor and predict human motions, monitor human breath, recognize five basic emergency hand signals, and indicate vital signs (Figure 4A).[117] It holds great potential for healthcare professionals to guide action-matched breathing, prevent patients from falling, and perform timely rescue measures. In addition, Paterson et al. developed a simple strategy for direct 3D printing of bioelectronic sensors on textiles using a very limited set of low-cost inks composed only of graphite flakes and silicone, thereby enabling accurate monitoring of hand functions involving records of simultaneous readings of pinch strength, thumb movement (flexion), and electromyography (EMG) of the abductor pollicis brevis muscle (Figure 4B).[118] 3D-printed devices provide objective, precise, and continuous data on the patient's function, movement patterns, and physiological responses, enabling healthcare professionals to accurately assess the progress of the patient's recovery. The development of such sensors will help in the development of personalized regenerative rehabilitation protocols.

Currently, the use of 3D printing for biomimetic fabrication seeks to recreate complex functions of natural organisms. Buchner et al. developed an inkjet-based multi-material deposition process termed vision-controlled jetting. This method uses contactless, continuous print adjustments to automatically create complex, functional systems and robots, offering a broader range of material families, elastic characteristics, high-resolution

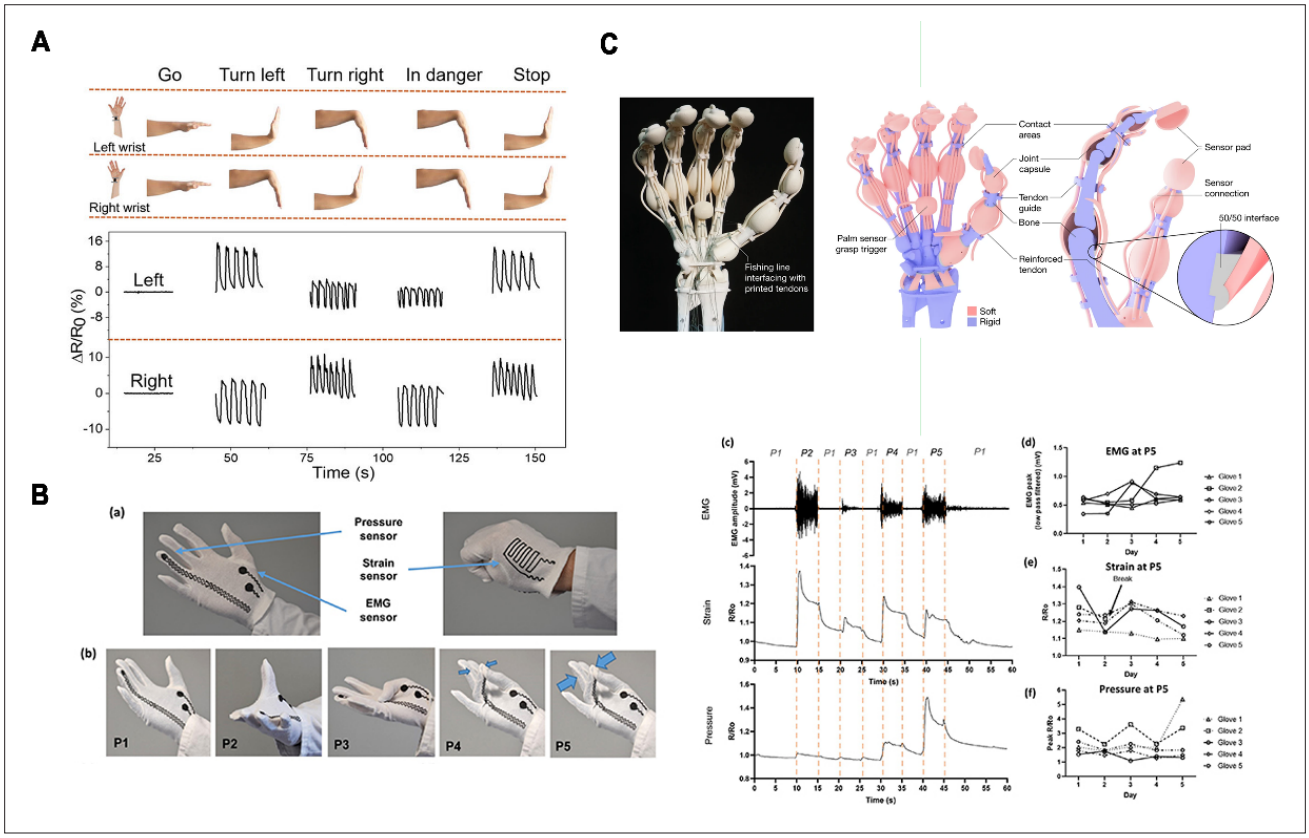

Figure 4. 3D-printed medical devices. (A) Discrimination of emergency signs based on two GC sensors worn on both wrists. Adapted with permission from Hou et al.[117] Copyright © 2023 The Authors. Reprinted under the terms of the CC-BY license. (B) 3D printed bioelectronic sensors for hand function monitoring. (B, a) Photographs of the fully printed gloves, displaying the placement and category of each sensor; (B, b) range of hand positions used during recording: P1, relaxed open hand; P2, thumb abduction; P3, thumb flexed across palm; P4, thumb and ring finger pinching with low force; P5, thumb and ring finger pinching with high force; (B, c) parallel sensor recordings of a typical glove, displaying the EMG of the abductor pollicis brevis and output of the strain and pressure sensors (vertical broken lines indicate the time when the hand assumes the indicated position); (B, d) peak of the low-pass filtered EMG burst; (B, e) peak resistance change of the strain sensor; (B, f) peak resistance change of the pressure sensor at P5 over the five sessions, with each glove individually tracked. Adapted with permission from Paterson et al.[118] Copyright © 2022 The Author(s). Reprinted under the terms of the CC-BY license. (C) A tendon-driven five-fingered soft-rigid hybrid gripper imitating a human hand printed in one process. Adapted with permission from Buchner et al.[39] Copyright © 2023 The Author(s). Reprinted under the terms of the CC-BY license. Abbreviations: EMG, Electromyography; GC, graphene nanoplate-carbon nanotube.

capabilities, and integrated actuation and sensing channels (Figure 4C).[39] This system was used to develop a multi-material tendon-driven hand, which is a fully functional print that is fitted with sensor pads and pneumatic signal lines. The tendon-driven hand can complete grasping actions autonomously, which may be beneficial for patients with physical disabilities to replace the fine motor function of hands. The potential of 3D printing technology holds significant promise for advancing the functional reconstruction of patients.

6. Clinical translation

Applying 3D printing technology in clinical practice still has some limitations. Firstly, health professionals should be educated and trained to improve acceptance and proficiency. Besides that, the absence of universally accepted testing standards poses a significant impediment to achieving consistent and uniform production of 3D-printed products. Notably, there is still a lack of clinical studies to verify the safety and efficacy of 3D-printed products in the clinical setting. Currently, clinical application research (data from www.ClinicalTrials.gov) demonstrates that the use of 3D-printed products for musculoskeletal diseases is mainly focused on orthoses and splints, with most of the studies concentrated in North America (Table 3; Figure 5). However, it is worth noting that clinical studies of 3D-printed scaffolds are still limited, despite the availability of commercially produced scaffolds using other methods in recent years.[13,119] Hence, greater emphasis should be placed on the clinical translation of 3D printing technology.

7. Conclusion

This review elucidated the transformative impact of 3D printing technologies on the workflow and therapeutic outcomes of musculoskeletal regenerative rehabilitation.

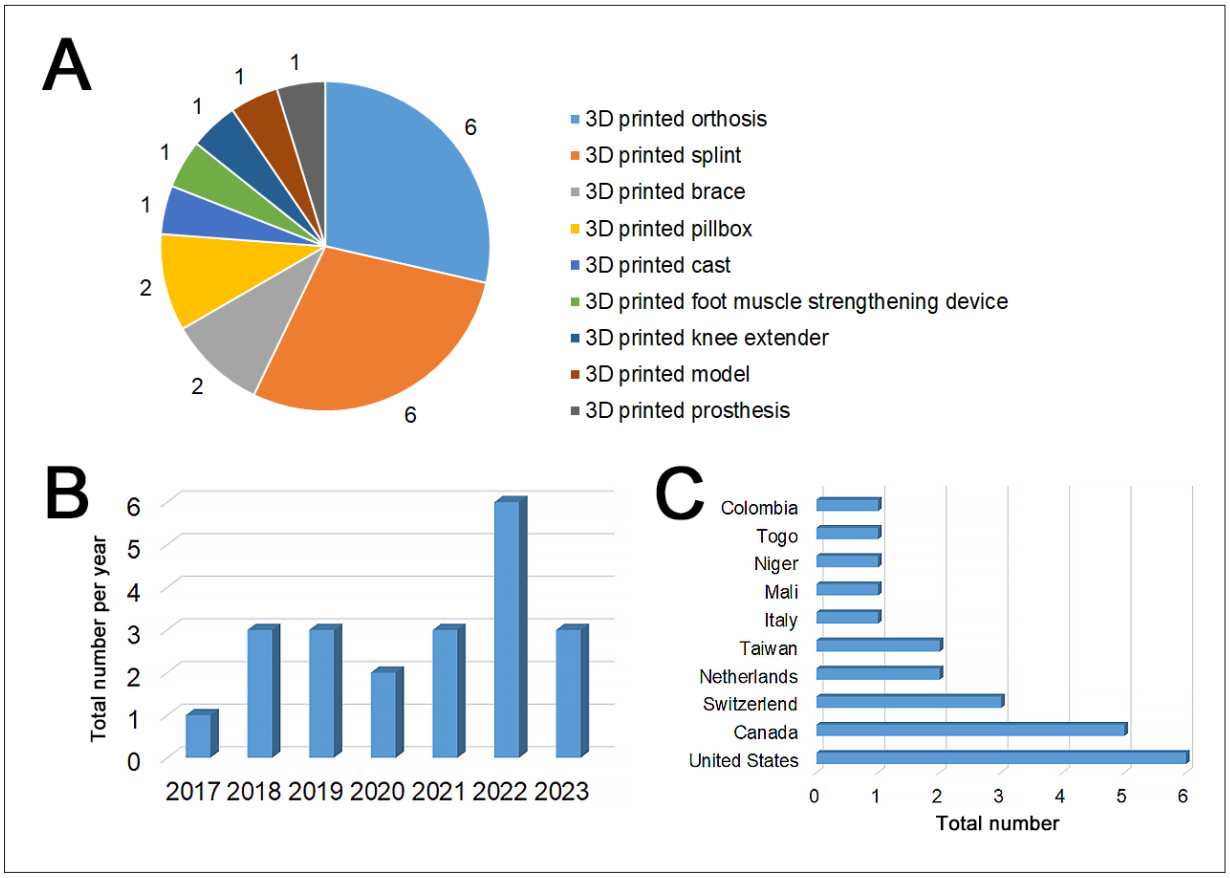

Figure 5. Statistics of the registered clinical trials of 3D-printed products for musculoskeletal diseases: (A) types of 3D-printed products for musculoskeletal diseases in registered clinical trials; (B) number of 3D-printed products for musculoskeletal diseases registered per year in the clinical trial registry system; and (C) the number of clinical trial registrations of 3D-printed products for musculoskeletal diseases around the world.

Table 3. Clinical application of 3D-printed products.

Application	Study title	Year	Type	Registration	Country	Design	Primary outcome
Scoliosis	A New Spinal Brace Design Concept for the Treatment of Adolescent Idiopathic Scoliosis	2018	3D-printed brace	NCT03365804	Canada	Single-blind RCT	Evaluated the in-brace Cobb angle on a radiograph
	Experimental Evaluation of Back Braces for the Treatment of Spinal Deformity Produced With 3D Printing Technology	2019	3D-printed brace	NCT04282408	Italy	Open-label, single-arm trial	Comfort and safety evaluation by using surveys
Distal radius fractures	Acceptability and Safety of 3D Printed Wrist-based Splints	2021	3D-printed splint	NCT05075135	Switzerland	Open-label RCT	Change in "Patient-Reported Splint Evaluation Questionnaire (PRSEQ)"
	A Clinical Comparison of Patient-Specific 3D Printed Splints Versus Conventional Splints in the Treatment of Distal Radius Fractures.	2023	3D-printed splint	NCT05902442	Netherlands	Open-label, single-arm trial	D-QUEST; CSD-OPUS; EQ-5D VAS; semi-structured interview
	Overnight and In-house 3D-printed Patient-specific Casts for Non-operative Treatment of Distal Radius Fractures	2020	3D-printed cast	NCT05346926	Switzerland	Open-label RCT	Score of modified patient satisfaction questionnaire; score of clinical effectiveness questionnaire
Sarcopenia	Foot Core Exercise Program on Balance Control and Walking in Aged Sarcopenia	2022	3D-printed foot muscle-strengthening device	NCT05750888	Taiwan	Quadruple-blind RCT	Sonographic imaging for the cross-sectional area of muscles; sonographic imaging for the width and thickness of muscles; balance test for standing posture for area of sway trajectory in CoP and CoM; balance test for standing posture for the velocity of sway trajectory in CoP and CoM; balance test for standing posture for the length of sway trajectory in CoP; functional walking test for spatiotemporal parameters; functional walking test for joint kinematics in the lower limb; functional walking test for joint kinetics in the lower limb; clinical questionnaires for assessment of physical capacity in the elderly; clinical questionnaires for assessment of functional capacity and falling condition in the elderly; clinical questionnaires for assessment of functional capacity and strength condition in the elderly

(Continued...)

Table 3. Continue...

Application	Study title	Year	Type	Registration	Country	Design	Primary outcome
ACL injury	Playmaker 3D Printed Knee Extender	2022	3D-printed knee extender	NCT05878652	United States	Triple-blind RCT	Knee extension range of motion; time to achieve full knee extension
Patient education	3D Printed Models in Mohs Micrographic Surgery	2018	3D-printed model	NCT03461965	United States	Open-label RCT	Percent of correct and incorrect Mohs quiz responses
Flat feet	Validation of Plantar Orthoses for Abnormal Plantar Arch Using a New Non-invasive Clinical Imaging System	2021	3D-printed orthosis	NCT05163418	Canada	Open-label, non-randomized trial	Change from baseline in the body's postural symmetry index at 2 months; change from baseline in the body's postural symmetry index at 6 months; change from baseline in the body's postural symmetry index at 12 months
Flexible flatfoot	The Effect of Customized Insoles on Biomechanics and Pain in Patients with Functional Flatfoot	2020	3D-printed orthosis	NCT04381039	Taiwan	Open-label, single-arm trial	F-scan system; visual analogue scale; foot function index
Hallux valgus	Dimensional Validation of the Hallux Valgus Orthosis	2021	3D-printed orthosis	NCT05163431	Canada	Open-label, single-arm trial	Change in big toe deviation angle during gait at 1 month; change in pain at 1 month; change in comfort at 1 month
Hand disease	New 3D Printed Wrist Orthosis	2022	3D-printed orthosis	NCT05597930	Canada	Open-label, randomized, crossover trial	Change in pain during treatment from baseline at day 14
Hand injuries and disorders	3D Printed Made to Measure Splints for Hand Patients	2019	3D-printed splint	NCT04306796	Switzerland	Open-label RCT	Change in patient comfort and satisfaction
	Three-dimensional Printed Hand Orthoses	2022	3D-printed orthosis	NCT05320211	Netherlands	Open-label, single-arm trial	Change from baseline in performance of ADL on the custom short form of the DF-PROMIS-UE at 4 months post-intervention
Orthopedic disorder	3D-printing and Access to Tele Rehabilitation	2018	3D-printed orthosis	NCT05947630	Mali; Niger; Togo	Open-label, randomized, crossover trial	10-m walk test; knee angle test; ankle angle test
Chronic disease	A 3D Printed Assistive Technology Intervention	2017	3D-printed pillbox	NCT03353038	United States	Open-label, single-arm trial	Incidence of treatment-emergent adverse events; QUEST2.0; ARMS
	Impact of Pillboxes on Medical Adherence	2019	3D-printed pillbox	NCT03861845	United States	Double-blind RCT	Medication adherence at 1 month; satisfaction with pillbox at 1 month; number of participants who completed the study

(Continued...)

Table 3. Continue...

Application	Study title	Year	Type	Registration	Country	Design	Primary outcome
Upper limb amputation below elbow	Redesign, Implementation, and Evaluation of the Effectiveness of the Aktio Myoelectric Prosthesis	2022	3D-printed prosthesis	NCT05510193	Colombia	Open-label, randomized, crossover trial	Functional status
Hand arthritis	Novel Splinting Technique Using 3D Models	2022	3D-printed splint	NCT05351060	United States	Open-label, single-arm trial	Change in range of motion of the hand (measured with a goniometer); change in range of motion of the hand (measured with a goniometer)
Hypermobility of interphalangeal joints	Splint Users' Satisfaction and Functional Status with Custom Finger Splints	2023	3D-printed splint	NCT05903391	United States	Single-blind, non-randomized controlled trial	Modified Orthotics and Prosthetics User Survey - Satisfaction with Device; Modified Orthotics and Prosthetics User Survey - Functional Status
Thumb osteoarthritis	3D-Printed Hand Orthosis Versus Thermoplastic Orthosis	2023	3D-printed splint	NCT05896410	Canada	Single-blind, randomized, crossover trial	Feasibility and general useability

Abbreviations: ACL, anterior cruciate ligament; ADL, activity of daily living; ARMS, adherence to refills and medications scale; CoM, center of mass; CoP, center of pressure; DF-PROMIS-UE, Dutch-Flemish Patient-Reported Outcomes Measurement Information System – Upper Extremity; QUEST2.0, Quebec User Evaluation of Satisfaction with Assistive Technology; RCT, randomized controlled trial.

Furthermore, we summarized the current landscape of clinical applications for 3D printing and discussed the clinical translation challenges of 3D printing. 3D printing technology can be seamlessly integrated with the protocols, principles, and technologies of both regenerative and rehabilitation medicine, driving a technological revolution in regenerative rehabilitation.

Looking ahead, the application of 3D printing in musculoskeletal disease treatment holds great promise for redefining regenerative rehabilitation interventions. Firstly, exploring the combination of 3D printing with novel physical therapies, such as pulsed electromagnetic fields (PEMFs), presents a holistic approach to systematic rehabilitation therapy. PEMFs are a bioelectromagnetic stimulation for bone and cartilage repair,[120–122] enhancing the growth and healing processes of the engineered cartilage.[123] Hence, 3D-printed products with novel physical properties can be formulated and utilized to enhance the overall rehabilitation effect in patients.[124] Furthermore, the integration of 3D printing with artificial intelligence (AI) can improve efficiency and accuracy. AI algorithms optimizing design processes, predicting material behaviors, and streamlining workflow showcase the potential to elevate 3D printing to new heights, fostering a seamless integration into routine clinical practice. In 4D printing, which incorporates "time" as the fourth dimension with 3D bioprinting, preprogramming smart materials enables the production of structures that dynamically react to external stimuli, adjusting their characteristics and functions for specific applications.[125,126] Moreover, AI has the potential to propel the transition from 4D printing to 5D printing, where AI will represent the fifth dimension.[125]

In summation, 3D printing is a rapidly advancing research field in regenerative rehabilitation for musculoskeletal disease treatment, demonstrating great potential for innovative approaches to evaluation, diagnosis, and treatment. With advances in new technologies and materials, we believe that 3D printing is crucial for accelerating the rehabilitation process and improving patients' quality of life.

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Conflict of interest

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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