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Review Article

Precision Bone Regeneration: 3D/4D Bioprinting of Personalized Hydrogel Scaffolds with Regenerative Cells and Adaptive Properties

Aanu Golapan Sureshkumar, Hema Prabha M. P., Pavazhaviji Pazhani*

School of Pharmaceutical Science, Vels Institute Of Science Technology & Advanced Studies (VISTAS), Pallavaram, Chennai, India.

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ABSTRACT

Critical-size bone defects remain a formidable surgical challenge worldwide, exacting a significant toll on patients' quality of life and functional recovery every year. Conventional treatment strategies autografts, xenografts, and synthetic substitutes continue to face major clinical limitations, and despite decades of progress in biomaterials and tissue engineering, this challenge persists because traditional scaffolds are inherently static, unable to adapt to the dynamic, multi-phase biology of bone healing. This review explores how the convergence of 3D bioprinting precision, 4D stimuli-responsive adaptability, hydrogel biocompatibility, and regenerative cell integration is reshaping bone regeneration into an intelligent, responsive process. Drawing on current literature evaluated across biomaterials, hydrogel chemistry, regenerative cell sources, fabrication techniques, scaffold architecture, porosity, mechanical performance, biodegradation, and biological outcomes, the evidence consistently shows that integrating these four technologies yields outcomes far superior to any single approach alone. Mechanistically, 4D-responsive scaffolds mirror the evolving extracellular matrix during healing softening in the inflammatory phase to promote angiogenesis and stiffening during mineralization to support new bone formation while hydrogel matrices simultaneously enable nutrient diffusion and sustained paracrine factor delivery essential for regenerative success. Together, these findings position 3D/4D bioprinted hydrogel scaffolds as a genuine paradigm shift, moving bone tissue engineering from passive structural support toward intelligent, adaptive regenerative systems poised for clinical translation within the next 5–10 years, with the potential to redefine the standard of care for complex bone defect reconstruction.

***Corresponding Author:** Pavazhaviji Pazhani
Address: School of Pharmaceutical Science, Vels Institute Of Science Technology & Advanced Studies (VISTAS), Pallavaram, Chennai, India
Email : pavazhaviji@gmail.com

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INTRODUCTION

Technological developments are dramatically impacting the evolution of healthcare. Treatment approaches are rapidly shifting from traditional, standardized approaches to more precise, customized ones. [1,7] About 178 million new bone fractures occur worldwide each year. Most of these fractures heal on their own, but 5 to 10% do not. These are called non-union fractures, which reduce quality of life. They are caused by biological variables such as osteoporosis, congenital abnormalities, and other ailments. [1,2] Bone scaffolds are three-dimensional biomaterial structures frequently used to treat bone defects. [8,13] They are intended to assist damaged or destroyed tissue to regenerate and heal itself. However, traditional scaffolds have serious limitations in adapting to the patient-specific needs and the constantly changing nature of bone healing. There is a significant and growing unmet clinical need for bone regenerative technologies.[1] More than 1 million bone grafting surgeries are performed each year in Western countries. The increasing need is mirrored in the orthopedic market with a tremendous growth from $15 billion in 2002 to $59 billion in 2023, pointing to the great therapeutic and economic value of bone tissue engineering. [1,4] Bone possesses an inherent power to regenerate itself, but this regenerative capacity is restricted to small defects. For large, complex bone defects, medical intervention is essential. The usual methods employed to treat bone defects are autografts, allografts, and xenografts, all of which have their own advantages and limitations. Problems may occur in these methods such as immune rejection, the risk of disease transmission, ethical issues, or the fact that patients are not in a position to have a second operation. [4,8,9] The characteristics of the scaffolds are mainly determined by the size of the pores, the porosity, the surface area, the surface area This has led to a need to develop advanced methods such as 3D and 4D printing, through which scaffolds can be designed according to the specific needs of the patient.[2,7,13] 3D printing is a digital fabrication process that allows a great freedom of geometry in the design and construction of lightweight structures, and allows shorter production times and thus material waste.[5,8,13] Four-dimensional printing, on the other hand, involves making the material responsive to stimuli so that it can adapt to the extracellular matrix of the bone at all stages of healing. [1,2,7,20,21] In order to achieve this, biolinks must be prepared, and for this purpose hydrogels as polymers are used since they are biodegradable and can adapt to their environment; they are therefore the preferred biomaterials for use in 3D and 4D bioprinting.[3,8] These hydrogels are water-rich polymers that mimic the extracellular matrix, support cell survival and provide controlled delivery of therapeutic agents.[3,14] They also protect the cells from being degraded when being injected. Natural or synthetic hydrogels can be used as composites to achieve biological function and mechanical properties.[8,14,15] Mesenchymal stem cells are multipotent and can differentiate into osteogenic, chondrogenic and adipogenic lineages and secrete paracrine signalling in the form of growth factors and cytokines to promote bone healing.[16,17] Recent evidence shows that integrated 3D/4D bioprinted hydrogel scaffolds containing regenerative cells achieve considerably better results: 60–75 per cent bone formation within twelve weeks (compared with 35–50 per cent with conventional scaffolds), accelerated vascularization by week six (as opposed to weeks 10–12), uniform mechanical integration, and fewer revision rates.[1,2,6,10] These improvements translate into better clinical outcomes including faster functional recovery, fewer complications, minimal donor site morbidity and improved quality of life. This review summarises the current evidence for the integration of 3D bioprinting, 4D responsiveness, hydrogel biomaterials, and regenerative cells for bone tissue engineering. [1,2,7] We review the significance of each component to regenerative capacity, the synergistic benefits of their combination, the challenges to clinical application, and the research directions for the future. Our aim is to provide an evidence-based perspective on the translation of integrative 3D/4D bioprinting into a clinical reality for bone regeneration.

2. Conventional Bone Grafting Approaches

Currently, there are four major types of conventional bone grafts. Different types have different characteristics, advantages and limitations affecting their clinical application in bone defect management. Autografts are bone materials taken from the patient's own body and

transplanted to the area that needs reconstruction. The iliac crest, tibia, calvaria, and mandibular ramus are all common donor sites. All bone grafts have three essential properties that make autografts the gold standard. These are osteogenesis, osteoinduction and osteoconduction. [4,9] The major disadvantage of autografts is the requirement of additional surgical procedures to obtain the bone from the patient, resulting in increased pain and morbidity. In addition, autografts may be inadequate in volume for complete reconstruction of large bone defects. Allografts are bone tissue obtained from another person of the same species and may be acquired from a cadaveric donor or from a living donor, such as excess bone removed during orthopaedic procedures. Allografts do not require donor site surgery, but they do carry significant risks, such as the risk of infection, transmission of disease, and immune rejection of foreign material. Xenografts are bone materials derived from different species, primarily from bovine and porcine sources. While xenografts provide an abundant supply of bone material, they raise substantial ethical concerns and present a theoretical risk of cross-species disease transmission to recipients. Alloplasts are synthetic, man-made materials designed to encourage bone growth. These materials are ceramics, polymers, metals and composite materials such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), bioactive glass, calcium sulphate, polylactic acid (PLA) and polycaprolactone (PCL). [8,13] Also they are biocompatible and have desirable physical properties, but they do not have the biological signaling to direct new bone formation.

3. Bone Structure and Composition

Bone is a living tissue that has a rich blood supply and plays many important roles in the body. It protects organs, holds essential minerals like calcium and phosphorus and helps the body stand upright by giving structure and support. Bone is made up of type I collagen, some -collagenous proteins and tiny mineral crystals called hydroxyapatite. These hydroxyapatite crystals are mostly made of calcium phosphate. Are what give bone its hard, stiff and strong nature. The structure of bone has layers and parts. The outside is covered with a layer called the periosteum, which's full of blood vessels and nerves. Under that is the cortical bone, a thick solid outer shell that gives bone its strength and helps it carry weight. Inside the bone there is bone, which is also known as spongy or cancellous bone. This part is lighter. Has a network of tiny struts. It helps with metabolic activities. Gives room for bone marrow to grow and function. Bone forms in the body through two ways. One is called ossification, where bone grows from a cartilage model. The other is ossification, where bone forms directly from mesenchymal tissue without going through a cartilage stage. Both of these processes are important for building bones during development and for healing bone after injury. Five key types of cells work together to keep bone healthy and to help it repair itself. Osteoprogenitor cells are, like a group. They can turn into other bone cells when needed. Osteoblasts come from stem cells and it makes a new bone material and lays down the bone matrix. Osteocytes are cells that started as osteoblasts. They help keep bone balanced and control how bone is rebuilt over time.Osteoclasts are derived from hematopoietic stem cells and can degrade bone tissue by releasing enzymes such as Cathepsin K and by producing an acidic microenvironment that demineralizes the bone matrix and degrades collagen. Bone lining cells are resting bone cells involved in the regulation of bone remodeling and the maintenance of bone homeostasis. During bone remodeling , or regeneration of bone , osteoclasts bind to damaged or aged bone and secrete proteolytic enzymes to digest the organic and mineral components of the bone matrix. At that time growth factors, like bone morphogenetic proteins (BMPs) and transforming growth factor-beta (TGF-β) are released into the surrounding area. These growth factors act as signals that draw precursor cells to the site where bone remodeling is happening. There they help these precursor cells change into mature osteoblasts. The osteoblasts then start making osteoid, which's the soft unmineralized part of bone. Over time this osteoid becomes hard. Turns into mature bone tissue. [8,13]

4. Bone Healing Process

Bone healing happens in two ways: primary and secondary. Primary bone healing happens when the fracture gap is smaller than 0.1 mm. Secondary bone healing happens when the fracture gap is bigger than

0.1 mm. Secondary bone healing is the common way bones heal. It has four steps: the hematoma stage, the fibro-cartilaginous callus formation, the bony callus formation and bone remodeling. After a break blood vessels burst and a blood clot called a hematoma form near the broken bone. This hematoma releases signals that start the healing process. The hematoma stage lasts one to five days after the break. During this time some cells called monocytes change into macrophages because of the signals. Macrophages are immune cells that can change what they do based on what is happening around them. This ability is called plasticity. In the part M1 macrophages, which are the type that causes inflammation do important jobs. They kill germs, clean up tissue, make signals like TNF-α, IL-1β and IL-6 and release harmful molecules. These actions help the bone to get better. Later M1 macrophages change into M2 macrophages, which help the body heal. This change is called polarization. It is an important step. M2 macrophages make a substance called VEGF, which helps make blood vessels. The second step is when a fibro-cartilaginous callus forms. This happens between five and eleven days after the break. Because of VEGF new blood vessels grow. At the time cells called fibroblasts make collagen and cells called osteoblasts start making early bone tissue. The third step is when the bony callus forms. This happens from eleven to twenty-eight days post-fracture. During this stage, the fibrocartilaginous callus is gradually replaced by a mineralized bony callus. The overall process is schematically represented in Figure.1. Osteoblasts continue depositing bone matrices while osteoclasts remove immature tissue to achieve proper structural organization. The fourth stage is bone remodeling, during which the mechanical strength of the bone increases and immature bone is remodeled into mature lamellar bone. [8,10]

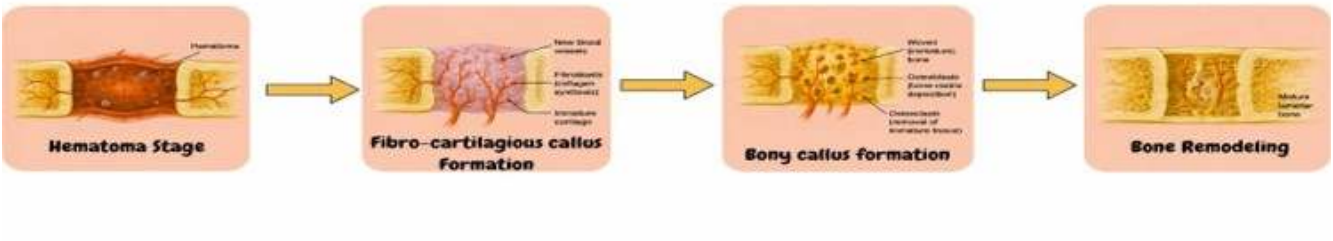

Figure 1: Schematic Representation of the Stages of Bone Healing

5. Mechanical Properties of Bone and Scaffold Architecture Considerations

The mechanical performance of bone depends on two structural components working in opposite but complementary ways. One is hydroxyapatite, the mineral of bones. It gives hardness, stiffness and resistance to the compression to the bone. This makes the bone strong and able to carry weight and stress. The other half is collagen, a protein that makes bone flexible and tough. It helps to stop cracking of the bone when bent or suddenly loaded. It is this combination of mineral and flexible organic material that gives bone its strength and ability to absorb energy without shattering. This balance is important for the design of scaffolds. A scaffold made from a hard ceramic may be strong under compression but it will be brittle. It will break easily under impact instead of bending or absorbing energy. On the other hand a scaffold made only from a soft polymer may be flexible but it will not have enough strength to hold up under normal body loads. That's why scientists are focusing more on creating scaffolds that blend ceramic and polymer materials. These combine the best of both worlds in one structure.

The compressive strength of bone ranges from about 100 to 200 MPa. Its tensile strength or resistance to pulling is usually between 50 and 150 MPa. These numbers vary between bone and cancellous bone, which have different structures and roles. Cortical bone has porosity about 5 to 10 percent and is dense, stiff and very strong. It forms the shell of bones and provides support and protection. Cancellous bone on the hand is much more porous between 50 and 90 percent and is less dense and less stiff. This high porosity is not a weakness. It is actually useful. The open connected

network of pores in bone allows space for blood vessels, bone marrow and the flow of nutrients. It also creates an environment for new bones to grow. [8,13] This dual nature of bone is one of the challenges in building scaffolds. A scaffold that is dense enough to support weight often has space for cells to move in or for blood vessels to grow. A scaffold that is very porous and allows cell migration usually lacks the strength to hold up under real conditions. To solve this problem the design of the scaffold must be carefully planned. The structure of the pores is key. Interconnected pores form paths inside the scaffold that let cells move, connect and build blood vessels. These pathways are essential for creating a blood supply encouraging tissue growth and keeping cells alive deep inside the scaffold. Vascularization or the formation of blood vessels is extremely important in scaffold design. Oxygen and nutrients can only reach cells by diffusion for about 100 to 300 micrometers from a blood vessel. Beyond that distance cells don't get what they need. They suffer from oxygen, lack of food and buildup of waste. In scaffolds without proper blood vessels the cells in the center quickly die. Without blood supply regeneration fails. So having a network of blood vessels inside the scaffold is absolutely necessary for healing bone defects. All these mechanical and biological needs shape what a bone scaffold must do. The structure of the scaffold needs to meet requirements at the same time. Pore size controls the space inside the scaffold. It determines which cells can enter and how well oxygen and nutrients can move through. Pore shape affects how cells attach, spread out and organize in the scaffold. Total porosity or how much of the scaffold is space, balances strength and biological function. Interconnectivity tells how well the pores link together. This affects whether cells and blood vessels can travel through the scaffold or get trapped in pockets. Wall thickness affects strength. Also, how close pores are to each other. Pore distribution describes how pores are arranged whether they are spread evenly or change in density from one area to another. Overall geometry refers to the shape and size of the scaffold, which must match the shape of the bone defect being treated. Getting the mix of all these features remains one of the hardest tasks in bone tissue engineering. Achieving an optimal balance across all of these architectural parameters remains one of the most demanding challenges in the field of bone tissue engineering and continues to drive advances in scaffold fabrication technology. [8,13]

6. Bone Tissue Engineering (BTE) Fundamentals

Bone tissue engineering (BTE) is being investigated as an alternative approach for repair of damaged or missing bone. It primarily involves the combined use of biomaterials, bioactive substances and regenerative cells to facilitate the formation of new bone tissue. [6,8] The need for this approach has increased due to several limitations of conventional bone grafting and scaffold-based methods. [1,4,8] Regeneration in traditional scaffolds is largely dependent on the ability of the patient's own cells to migrate into the scaffold, proliferate and differentiate into bone-forming cells. The scaffold itself usually has fixed properties after implantation. For example, its porosity, mechanical strength, architecture, degradation rate, and surface properties cannot readily change according to the conditions of the surrounding tissue.[8] However, bone healing is not a static process; the requirements of the tissue change continuously as healing progresses. Thus, a scaffold with permanently fixed properties might not always be a proper support during the whole regeneration process. A scaffold with a good balance between biological and mechanical properties is required for successful bone regeneration. It has to be biocompatible so that it can support cell growth without triggering an undesirable immune response. The porous structure should enable cell ingress to the scaffold and to allow flow of the oxygen and nutrients. The scaffold should also be mechanically stable enough to sustain the environment at the defect site, while providing temporary support of the newly regenerating tissue. At the same time, it should degrade slowly at a suitable rate, so that the newly formed bone can replace the scaffold over time. In addition to these properties, the scaffold should be osteoconductive and ideally provide cues that drive osteogenic differentiation. Realization of all these requirements within a single scaffold is a great challenge in bone tissue engineering. To overcome these limitations, researchers have increasingly focused on the development of scaffolds that mimic the natural

extracellular matrix (ECM) of bone.[8,14] Such scaffolds can provide a more suitable environment for cell attachment, migration, proliferation and differentiation. Hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), polycaprolactone (PCL) and polylactic acid (PLA) are materials widely studied in the fabrication of bone scaffolds. Bioactive molecules including bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF) can be incorporated to enhance their performance. These molecules play an important role in osteogenesis and angiogenesis, respectively. Regenerative cells commonly include mesenchymal stem/stromal cells (MSCs), bone marrow-derived stem cells, dental pulp stem cells, adipose-derived stem cells, and osteoblasts. In this particularly mesenchymal stem cells (MSCs), including bone marrow-derived MSCs, can also be incorporated into these systems.[16,17] These cells have the ability to differentiate toward Osteoblasts and can release signaling molecules that support new bone formation and vascular development.

6.1 Regenerative Cells as Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) release paracrine factors including growth factors, cytokines and other signaling molecules, which deliver powerful signals to neighboring cells, regulate the local tissue microenvironment, and promote bone repair. However, two major problems arise with MSCs after implantation. Excessive inflammation and immune responses can cause cell damage at the site of injury. Second, phenotypic plasticity may take place, with MSCs differentiating into undesired cell types and not into osteoblasts.[16,17] To address these issues, composite scaffold based approaches have recently incorporated bone marrow derived mesenchymal stem cells into hydrogels such as GelMA combined with structurally supporting PCL/hydroxyapatite (PCL/HAp) scaffolds.[3,16] MSCs have a high biological and regenerative potential, but the clinical efficacy strongly depends on the design of the cellular and biomaterial environment. Recent studies have also shifted to exploiting extracellular vesicles (MSC-EVs), including exosomes, derived from MSCs as a cell-free regenerative approach. With this approach, MSC implantation is avoided altogether. In contrast, EVs are detached from MSCs and mounted onto scaffolds, which reduces the likelihood of uncontrolled cell behavior and does not demand cell survival after implantation. These EVs carry proteins, RNA and lipids that signal to recipient cells and mediate regenerative effects without the issues associated with live cell transplantation.[22]

The development of 3D printing has opened up new avenues for overcoming some limitations of conventional scaffold fabrication. In 3D printing, the structure of a scaffold can be designed with greater precision and features such as pore size, porosity, shape and internal architecture can be tuned to the needs of a specific bone defect. The integration of patient-specific imaging data with computer-aided design also allows for the fabrication of scaffolds that closely match the shape of an individual defect. This can improve scaffold fit and better support tissue regeneration. But conventional 3D printed scaffolds are typically not modified after implantation. Although the biological environment surrounding the scaffold is still evolving during the healing process, their structure and properties are largely pre-determined during fabrication. This limitation has caused increased interest in 4D printing. In layman's terms, 4D printing adds a dynamic or time-dependent element to the 3D-printed structure. The stimuli-responsive materials allow the design of the printed scaffold to change in shape, mechanical properties or function in response to specific stimuli. Depending on the material, these reactions can be induced by temperature, pH, light, magnetic fields, electric signals, or biological factors. This makes the 4D-printed scaffolds different from conventional static scaffolds in the sense that they have the potential to respond to their environment and adapt as the regeneration process progresses. Therefore, 4D printing might contribute to transforming bone tissue engineering from the idea of a passive scaffold to a more active and responsive way of tissue regeneration. Hydrogels can be especially useful in these systems because their water-rich, three-dimensional structure can provide an environment that mimics some features of the natural ECM. When embedded in a hydrogel, the material can provide a supportive environment and help protect the cells from mechanical damage during processing and fabrication. It may also promote cell survival and provide a favorable environment for cell proliferation and

differentiation. Hydrogels can also enhance the delivery of nutrients and oxygen depending on the composition and can be used to carry growth factors or other bio-active substances to the site of regeneration. Combining hydrogels with regenerative cells and 3D or 4D printing therefore provides an opportunity to create scaffolds in which the structural and biological components work together.[16] Thus, the combination of regenerative cells, hydrogels, bioactive materials, and 3D/4D printing is emerging as an important area in bone tissue engineering. 3D printing offers precise control over the shape, architecture, porosity, and mechanical properties of the scaffold, while 4D printing adds the possibility of time-dependent adaptation in response to environmental stimuli. The long-term aim is to develop a scaffold that can provide adequate support during the early stages of bone healing, create a favorable environment for cell and blood vessel formation, and eventually degrade as new bone develops. Such approaches could provide a more adaptable and personalized strategy for the regeneration of complex bone defects.

7. Biomaterials for Bone Scaffolds

An ideal bone scaffold must be biocompatible, biodegradable, mechanically strong, bioactive, osteoconductive, and suitable for fabrication that supports vascularization, cellular infiltration, and extracellular matrix deposition. A biomaterial is inserted into the body to replace support or regenerative damaged tissue. Therefore, the structural, mechanical, and biological features cannot be fully replicated by a single biomaterial. Thus, the following articles will discuss metals, ceramics, natural and synthetic polymers, and their composites that have been studied as scaffold materials. Collagen, gelatin, chitosan, silk fibroin, hyaluronic acid alginate, and other natural polymers are produced from proteins and polysaccharides as they facilitate tissue regeneration and favorable cellular contact. One of the main components of the extracellular matrix of natural bone is collagen, which carries biological cues that promote osteogenic activity and cell adhesion. Their immunogenicity is comparatively poor. These polymers have several disadvantages, such as low mechanical strength, poor degradation, batch-to-batch variability, and restricted processability. Therefore, rather than being employed on their own, natural polymers are frequently combined with synthetic polymers or inorganic phases.[8,13,14] Inorganic materials called ceramics are employed in bone scaffolds because they resemble the mineral components of bone. The hydroxyapatite, which has calcium and phosphate as its main constituents, is significant. HAp has a significant impact on the mechanical strength of these ceramics because they have strong biocompatibility, bioactivity, and osteoconductivity, which promote cell adhesion and are appropriate for bone formation. However, the brittleness of ceramic materials continues to be a major disadvantage. In bone tissue engineering, metal biomaterials are utilized because they offer more mechanical strength and toughness than polymers and ceramics. metals such as titanium. Robust, non-corrosive, and biocompatible, making it inert; nonetheless, it is not biodegradable and requires a separate surgical procedure to be removed from the body. Additionally, biodegradable metals that break down as tissues develop are used, such as iron, zinc, and magnesium. However, because magnesium corrodes readily, they will be coated to slow down the process. The rationale behind this is the creation of composite scaffolds combining two or more materials to generate complimentary qualities and negate the disadvantages of individual components. For instance, a material with low mechanical strength can be reinforced by a material with superior mechanical properties. Likewise, other drug delivery methods can be incorporated in the polymeric scaffolds to have controlled or sustained release of drugs, while providing other therapeutic effects such as antimicrobial and wound healing capabilities. In recent years, natural plant-derived materials have gained more attention in the development of scaffolds because of their biocompatibility, biodegradability and potential bioactive properties. For example, banana pseudostem fiber, rich in cellulose, has been integrated into polymeric hydrogel matrices to improve their functional and structural properties for tissue engineering applications such as wound healing and bone regeneration.

8. Hydrogel Based- Bone scaffold

Hydrogels are a class of three-dimensional polymeric biomaterials with high water content and have been

shown to be versatile scaffolding materials for bone regeneration.[3,8,14,15] Due to their water-rich structure and structural similarity to the ECM, they are ideal candidates for a variety of applications ranging from drug delivery to wound healing and tissue engineering. [3,14] Apart from their structural characteristics, hydrogels provide a physiologically relevant microenvironment that actively promotes cell adhesion, migration and osteogenic differentiation, all of which are critical processes for successful bone regeneration.

8.1 Composition and Classification of Hydrogel Polymers

Hydrogels are composed primarily of water, which comprises 70–90% of the total material volume. This high-water content facilitates the diffusion of essential nutrients, oxygen, waste products, and therapeutic agents throughout the hydrogel matrix, a prerequisite for cell survival in the scaffold interior. This property distinguishes hydrogels from more rigid biomaterials and makes them particularly suitable for sustaining cellular activity within three-dimensional structures. Hydrogel polymers are broadly classified into two categories: Natural polymers, Synthetic polymers. Natural hydrogel polymers include collagen, gelatin, hyaluronic acid, alginate, and chitosan. These polymers are derived from biological sources and inherently possess biocompatibility and cellular recognition properties. Collagen and gelatin, for example, contain peptide sequences that cells recognize through integrin receptors, promoting adhesion and migration. Hyaluronic acid is naturally present in the bone ECM and strongly stimulates cell interactions. Alginate, derived from brown seaweed, is non-immunogenic and readily crosslinkable. Chitosan, extracted from crustacean shells, provides antimicrobial properties alongside biocompatibility. [8,14,15] Synthetic polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), polylactic acid (PLA), and polycaprolactone (PCL) offer the advantage of reproducible properties and tunable degradation kinetics. Unlike natural polymers, synthetic variants permit precise control over molecular weight, crosslinking density, and mechanical properties, enabling rational design of scaffolds with predetermined characteristics. [8,15] This controllability has made synthetic polymers increasingly valuable for advanced tissue engineering approaches.

8.2 Functional Properties and Drug Delivery of Hydrogel-Based Scaffolds

The success of hydrogels in bone regeneration is governed by a combination of physical and chemical properties that are dictated by the topology and the type of cross-linking of the polymeric network. [3,18,14] Hydrogels physical properties include mechanical strength, porosity, swelling capacity, water content, elasticity and degradation behavior. Among them,

porosity is probably the most biologically relevant parameter. The interconnected pore network within a hydrogel directly controls cell vascularization, cell migration, and the diffusion of signaling molecules throughout the scaffold interior. Physical crosslinking occurs through weak, reversible interactions including hydrogen bonding, ionic interactions, hydrophobic interactions, and van der Waals forces as these interactions are reversible and dynamic, physically crosslinked hydrogels are generally softer, more flexible, and capable of undergoing structural changes in response to environmental conditions. This reversibility is advantageous for cell-seeding procedures but can be disadvantageous for long-term mechanical stability. In contrast, chemical crosslinking involves the formation of covalent bonds between polymer chains, resulting in higher mechanical stability and more predictable degradation kinetics. However, some chemical crosslinking methods require initiators that may produce cytotoxic byproducts if not adequately removed during purification, a consideration that must be carefully addressed to ensure cell safety. The hydrogel's ability to absorb and retain water is a double-edged property. While moderate swelling creates the porous, cell-friendly environment essential for regeneration, excessive swelling leads to loss of mechanical strength and structural integrity, potentially compromising the scaffold's load-bearing capacity at the defect site. Balancing these competing demands represents a central design challenge in hydrogel development. [14,25] The mechanical properties of hydrogels including stiffness, strength, elasticity, viscoelasticity, stress relaxation, and fatigue resistance profoundly influence their suitability for bone applications. Native hydrogels are considerably softer than cortical bone. This mechanical mismatch can be addressed through multiple strategies: increasing polymer concentration, enhancing crosslinking density, and incorporating inorganic particles such as nanofibers or HAp. The incorporation of reinforcing phases has been especially successful; composite hydrogels combining alginate or gelatin with β-TCP, bioactive glass, hydroxyapatite or other calcium phosphate phases display significantly improved mechanical properties and increased osteogenic potential. These composites address the challenge of reconciling the biological functionality of soft hydrogels with the mechanical requirements of load-bearing applications. One of the most valuable properties of hydrogels is their ability to carry therapeutic agents and release them in a controlled manner. Hydrogels can incorporate small molecule drugs, peptides, and growth factors either by physical encapsulation or covalent conjugation. These agents are released upon scaffold hydration and swelling at the implant site following the degradation profile and diffusion properties of the hydrogel. This controlled release mechanism gives a lasting targeted treatment that works much better than giving medicine all through the body when trying to help the bones grow in a specific place. Hydrogels are better materials for making new bones than other methods. They have a lot of water, they look like the structure of the body, they can be changed to have different strength and chemistry and they are great for using in new 3D and 4D printing techniques. These features make them the best choice, in the field of healing the body. As the machines that print things get better and the way we make hydrogels gets more advanced these materials will help create treatments that're more exact and more powerful.

9. Three-Dimensional (3D) Printing in Bone Tissue Engineering

Thousands of people wait every year for the suitable organ for transplantation and thousands die waiting for the suitable organ. This widening gap draws attention towards the clinical need. This is where 3D printing comes in which creates a personalized patient specific scaffold along with the deposition of the living tissues into the biomaterial. In tissue engineering the cells are cultivated or embedded inside the scaffold there are some significant bottleneck issues like inadequate vascularization through which the nutrients and oxygen supply will be restricted. This facilitates the advancement of the vascularized system in 3D printing. The 3D printing happens with the help of the polymer along with the tissue cells embedded in it. In which they are called as the bioinks were brought into advancement Bioprinting technologies have progressively diversified into several distinct modalities, such as inkjet-based, extrusion-based, laser-assisted, and stereolithography-based bioprinting.[12,19] In terms of resolution capabilities, inkjet bioprinting is one of the

leading technologies since it is driven by the same principles as inkjet printers and enables accurate placement of bioinks with cells and biomolecules, especially in high-resolution settings. Extrusion-based bioprinting is one of the most widely popular techniques, which is capable of precisely controlled deposition of highly viscous bioinks to nozzles, which in turn enables the construction of complex tissue architectures. On bioprinting the cells undergo stress which leads to the cell death stereolithography based bioprinting enables the cell placement accuracy without mechanical stress also importantly vascular network. Composite hydrogel scaffolds are made which provide good mechanical strength. [12,14]

9.1 Fundamental principles and fabrication techniques

3D bioprinting is a sophisticated additive manufacturing technology that precisely deposits bioinks containing living cells and biomaterials layer by layer, based on a computer-generated model, to accurately produce three-dimensional tissue constructs. The main bioprinting techniques are: inkjet-based, extrusion-based, laser-assisted and stereolithography-based bioprinting. They differ in the way they deposit and solidify the bioink. In the case of inkjet bioprinting the bioink is dispensed in the form of droplets without direct contact, mostly using thermal or piezoelectric actuation. Thermal actuation creates bubbles by rapid heating, while piezoelectric actuation relies on the deformation of a piezoelectric crystal after electrical stimulation to create pressure pulses that eject droplets.

Piezoelectric systems do not expose the cells to heat, and allow high resolution deposition. However, viscosity constraints and shear stress during the ejection of droplets may affect the viability of the cells. One of the most common techniques is extrusion-based bioprinting, in which bioink-containing cells are deposited in continuous strands through a nozzle using pneumatic, piston-driven or screw-driven mechanisms to construct larger and more complex structures.[12] Bioinks need to have suitable rheological properties, especially shear-thinning behavior, to enable easy extrusion and shape fidelity after deposition. Suitable physical or chemical cross-linking is also required to provide structural stability. Laser-assisted bioprinting (LAB) relies on laser-induced forward transfer to accurately place droplets of bioink with cells onto a receiving substrate. The absence of nozzles and low shear stress enable LAB to produce high cell viability, high cell density, high printing speed, and accurate spatial positioning of cells. However, LAB requires expensive and sophisticated equipment and careful control of laser parameters. Conversely, bioprinting based on stereolithography (SLA) utilizes light to selectively polymerize layer-by-layer photosensitive bioinks. The computer-aided design (CAD) model is sliced into thin layers, each of which is selectively exposed to UV or visible light to solidify the material, allowing the fabrication of highly complex structures with high resolution and surface detail. [5,13] However, the development of biocompatible and biodegradable photopolymerizable materials and the potential effects of photo initiators and light exposure on cell viability are still important challenges. To summarize, these technologies have many merits such as resolution, printing speed, cell viability, bioink compatibility, structural complexity, and mechanical properties, which enable the researchers to choose the most suitable technique according to the requirements of tissue engineering and regenerative medicine.

9.2 Bioprinted Scaffold Fabrication

Bioink is a material which is loaded into the bioprinter which consists of the living cells and the composite form of the biomaterial. The biomaterial can be natural or synthetic or the combination of both. [2,5,13] The rheological properties needed to be considered like viscosity, shear thinning, printability so the flow property can be optimized. The living cells such as mesenchymal stem cells are incorporated into bioink under sterile condition. Ensure evenly distributed, present in an appropriate cell density and cell viability. [2,5] The bioinks are loaded inside the bioprinter and the CAD Software determines the shape of the scaffold based on the patient's compliances. The printer parameters such as nozzle diameter, extrusion pressure, temperature, printing speed. Immediate after or during the printing to provide the stability for the printed material, crosslinking is done. Figure.2. Illustrates the Flowchart of the Bioprinting for Functional Scaffold Development.

There are different types of crosslinking, Ionic crosslinking, Photo crossing, Thermal crosslinking, Enzymatic crosslinking. [3,5,14] After tissue embedded into the scaffold it should be incubated in culture media so the tissues can adapt to the media and cells begin producing ECM which is essential for developing tissue

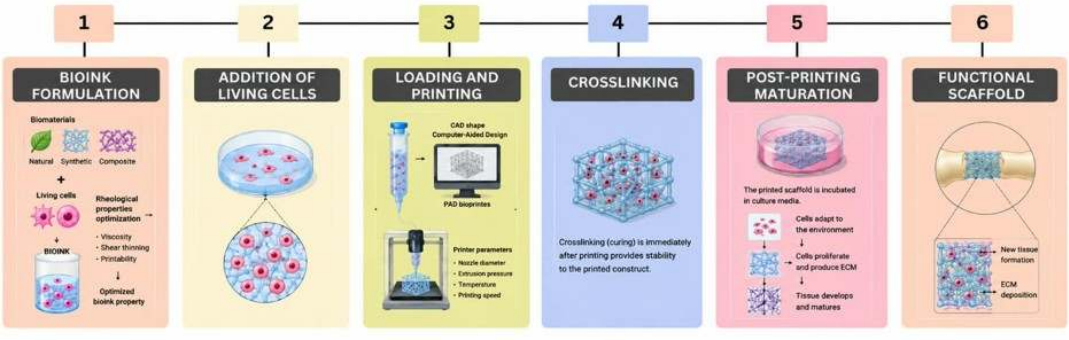

Figure 2: Flowchart of the Bioprinting for Functional Scaffold Development

10. Four-Dimensional (4D) Printing: Next-Generation Scaffolds

4D bioprinting is an advance in the field of bioprinting that adds temporal elements to conventional 3D bioprinting. [1,2,7,19] The difference between 3D and 4D in the 4D engineering of the material which can respond to the external stimuli and can change their properties. A comparative overview of these materials is provided in Table 1. The smart stimuli responsive hydrogels like polymers are made which respond to applied changes in temperature, pH, basicity/acidity of the environment or light. They are also known as dynamic scaffolds. [20,21] Although many advances have been made in the field of 4D bioprinting, there are still challenges that need to be addressed. These include the development of more advanced bioinks, the optimization of printing conditions, and clinical translation of 4D bioprinted materials. These materials add a fourth dimension to the traditional 3D-printed structure, time-dependent transformation. In 4D bioprinting that is sensitive to humidity, materials can swell and change shape when exposed to water or moisture. For example, alginate and hyaluronic acid-based hydrogels can be printed as flat films and they can spontaneously fold into tubular structures upon immersion into water. The degree of folding can be controlled by factors like the cross-linking gradient, printing angle, layer thickness, and cross-linking time. Temperature Responsive Materials Temperature responsive materials change their volume or shape upon a change in temperature. The pNIPAM is a thermoresponsive polymer that has been extensively explored due to its reversible swelling and shrinking behavior around its lower critical solution temperature (LCST). In the same way, materials that are responsive to electrical and magnetic stimuli can respond by changing their shape or function. [20,21] Conductive polymers such as polythiophene, polyaniline and polypyrrole can respond to stimulation. In addition, magnetic-responsive hydrogels can change their volume when a magnetic field is applied. This deformation can be used for controlled drug or cell release by pushing fluid out of the scaffold pores. Therefore, the incorporation of these materials allows 4D-bioprinted constructs to adapt dynamically to their surroundings. 4D-bioprinted constructs then offer functionality for applications in tissue engineering, regenerative medicine and controlled drug delivery. Although 4D bioprinting technology has shown results in research settings there are still major obstacles when moving 4D bioprinting from the lab to the clinic. One key problem is that the fabrication methods for 4D bioprinting are still being developed and there is no standard. Because 4D-printed scaffolds are made specifically for each patient's anatomy the production of 4D-printed scaffolds becomes more complex and costly. The integration of advanced technologies bioprinting equipment, stimuli-responsive materials, biocompatible polymers, growth factors and living cells adds to the cost of 4D bioprinting making it difficult for 4D bioprinting to be affordable and accessible enough for widespread use, in clinical practice.

Table 1: Comparative Assessment of Scaffold Fabrication Strategies: Conventional, 3D and 4D Printing

Parameters	Conventional scaffold	3D-printed scaffolds	4D-printed scaffolds	References
Fabrication	Non-3D-printing techniques like solvent casting, freeze-drying, and gas foaming	3D structures that mimic the extracellular matrix and support cell growth	Smart, programmable materials that change their shape, size, or function over time when exposed to specific triggers like heat, moisture, or light	[23,24,25]
Mechanical properties	Limited and hard-to-control mechanical properties	Depend heavily on their internal architecture, printing direction, and material composition	Depend heavily on smart-material selection, porosity, and programmable structural transformations over time.	[26,27]
Pore size and interconnectivity	Often irregular and difficult to control	Precisely designed and interconnected	Can potentially change in response to stimuli	[8,28]
Hierarchical architecture	Difficult to reproduce natural bone hierarchy	Can mimic macro-, micro- and nanoscale features	Integrates multi-scale structural designs with time-dependent, programmable shape transformations	[29,31,30]
Patient-specific geometry	Limited	Highly customizable using medical imaging/CAD model	Highly customizable with dynamic changes	[13,7]
Cell migration & vascularization	Dependent on randomly formed pore networks	Controlled interconnected pores facilitate cell and vessel infiltration	Dynamic architecture may provide an adaptive cellular environment	[32,31,33]
Biological response	Mainly provides a static environment	Can incorporate cells, drugs or growth factors depending on technique	Can provide stimulus-responsive or time-dependent biological functions	[32,31,34]

CONCLUSIONS

There is an ongoing paradigm shift in the bone tissue engineering area towards intelligent adaptive regeneration systems.[7] The combination of 3D bioprinting, 4D responsiveness, hydrogel biomaterials and regenerative cells can be considered as a breakthrough approach allowing for addressing the shortcomings characteristic for conventional bone grafts and scaffolds. The combination of these elements results in better effects in comparison with any particular technology.[2] The most important point is that these improvements are beneficial for a patient's health: faster recovery, no donor site morbidity, reduced pain and complications.[17] Despite these revolutionary achievements, substantial hurdles in the way of translation into practice exist.[2,19] The Fabrication process is not standardized, bioprinting techniques vary among labs and pose potential challenges to reproducibility and regulation. High cost of manufacturing associated with personalization of the design and integration of multiple technologies continues to prevent wide access for the majority of patients. Regulatory pathway for combination products (device, biologic, and drug) is not fully developed causing delay in approval process. Data on long-term biocompatibility and safety in humans is still being collected and clinical trials should be completed within 18-24 months from now.[17]

In order to address these barriers in the future it is necessary to develop coordinated efforts in different spheres. Automation and standardization of the bioprinting process will lead to better reproducibility and

reduced cost. [2,5] Rational design of the scaffold through computational optimization will eliminate the need for empirical validation of the product. Scale up and standardization of the manufacturing process will further lower the cost and allow it to reach parity with conventional technology within 5-10 years. Regulatory coordination between countries will solve the problem of combination products approval. Finally, clinical trials will provide the data needed for long-term safety and efficacy of the product. In the next decade, 4D bioprinted hydrogel scaffolds seeded with regenerative cells will become standard care for complex bone defect reconstruction. [1,16,17] Transformation from reactive and limited to proactive, personalized, and adaptive regenerative medicine represents not only technological progress but also revolution in how medicine restores the tissues. With development of the technology and overcoming the obstacles, the prospect of true biological regeneration becomes achievable reality.

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