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To cite this article: Cem Alparslan and Şenol Bayraktar 2026 *Surf. Topogr.: Metrol. Prop.* **14** 013003

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## TOPICAL REVIEW

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RECEIVED  
8 July 2025

REVISED  
13 October 2025

ACCEPTED FOR PUBLICATION  
4 February 2026

PUBLISHED  
26 February 2026

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## Additive manufacturing in biomaterials: a comprehensive and integrated review of innovations in tissue engineering, bioprinting, implant design, and regenerative medicine

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**Keywords:** additive manufacturing technologies, biofabrication, hydrogels, tissue regeneration, personalized biomedical implants, polymer–ceramic composites, 3D bioprinting in medicine

### Abstract

Additive manufacturing (AM) has rapidly evolved into a groundbreaking technology in biomedical engineering, offering unprecedented capabilities for fabricating patient-specific, anatomically complex structures with high precision. This review presents a comprehensive and critical overview of recent innovations in AM-applied biomaterials, focusing on the integration and application of hydrogels, biopolymers, ceramics, metals, and composite systems. These materials, each with unique biological and mechanical attributes, are pivotal in advancing regenerative medicine, tissue engineering, and the development of next-generation medical implants and devices. Special emphasis is placed on hydrogel-based bioinks and photopolymerizable networks used in 3D bioprinting, which offer tunable properties, excellent biocompatibility, and the ability to mimic extracellular matrix environments. Furthermore, the synergistic design of structural and functional materials in AM platforms is explored to address critical challenges such as mechanical durability, degradation kinetics, immunomodulation, and dynamic cell–matrix interactions. By synthesizing current progress in material science, biofabrication strategies, and translational pathways, this review highlights the transformative potential of AM in shaping the future of personalized and precision medicine—bridging the gap between innovative material design and clinically viable biomedical solutions.

### 1. Overview of additive manufacturing in biomedical engineering

AM has emerged as a transformative technology in biomedical engineering, turning concepts that were once theoretical into practical applications. Today, with the development of technology, AM in biomedical applications has created a significant revolution, mostly in the fields of health and medicine. AM is a modern manufacturing technology that allows the production of complex and personalized products [1] such as implants [2], tissue engineering structures [3], and biomedical devices [4]. This manufacturing method creates a physical object by adding materials layer by layer from a digital 3D model.

ASTM-F42 Committee defined AM as a process of joining materials to make objects from 3D model

data, usually layer on layer, in contrast to traditional manufacturing technologies [5]. This technology was developed for rapid prototyping and has become one of the modern production methods. First developed in the late 1980s, the AM method was preferred to accelerate design processes and test the functionality of new products [6]. Early methods of AM technology include SLA (Stereolithography) [7] and fused deposition modelling (FDM) [8, 9]. These production techniques were developed and used primarily to produce simple models and prototypes with polymer materials. With the development of computer-aided design (CAD) software since the early 2000s, the field of AM applications has expanded and different methods have begun to emerge. The need for various materials in part production has increased day by day and it has become important for production methods to

manufacture more complex geometric structures with high precision. This has caused AM technology to move from rapid prototyping production to industrial part production and even biomedical applications.

In these years, the use of laser technology has begun to increase in AM methods. Advanced techniques such as selective laser melting (SLM) and direct metal laser sintering (DMLS) technologies have been developed, where metal powders are used and metal parts are built layer by layer [10]. These methods enabled the production of functional and durable products in sectors requiring high precision, such as aviation, automotive, and biomedical engineering. This marked a significant step in the advancement of AM technologies [11, 12]. The importance of AM technologies, especially in the biomedical field, has begun to increase and has been identified as an ideal solution for personalized prostheses [13], implants [14], and medical devices [15] that are difficult to manufacture with traditional manufacturing methods. First used in orthopedics and dental technology, AM technologies have gradually shifted to more complex and innovative areas such as tissue engineering, bioprinting and organ simulations. Thanks to bioprinting, the production of organ-like structures using biomaterials and living cells has provided alternative solutions for patients awaiting organ transplants [16–19]. Thus, AM technology has developed with the ability to produce structures that fully adapt to the individual anatomical structure of patients. This has made it possible to develop patient-specific treatment solutions and personalize biomedical devices [20–23].

In the future, it is expected that advanced applications such as printing cell structures and organ production will become widespread thanks to the developments in the field of AM technology in the health field. Thanks to this situation, the importance of AM technologies in the medical and biomedical fields will increase even more and will lead to revolutionary changes in health care [24, 25]. In this context, this review article aims to comprehensively address the current status, potential and challenges of AM technology in biomaterial applications. The study focuses on the roles of different types of biomaterials such as polymers, ceramics and metals in AM processes; application areas such as tissue engineering, implant design, biosensor production and bioprinting are examined in detail. In addition, opportunities and obstacles in the transition of these technologies to clinical applications are evaluated and suggestions for future research directions are presented. The potential of AM technology to revolutionize biomedical engineering is the focus of this article.

This study conducted a literature review using a specific methodology. The Scopus, Web of Science, and PubMed databases were used during the review process, and searches were conducted using the

keywords ‘additive manufacturing,’ ‘3D printing,’ ‘biomaterials,’ ‘scaffold,’ ‘tissue engineering,’ ‘regenerative medicine,’ ‘bioprinting,’ and ‘implant.’ The search was limited to publications between 2015 and 2025. Inclusion criteria included publications in peer-reviewed journals, written in English, and covering AM processes directly or indirectly related to biomedical applications. Exclusion criteria included conference proceedings that focused solely on industrial production, lacked a biomedical context, or had limited accessibility. Approximately 435 studies were initially identified, and 181 articles were included after a screening based on the criteria. This approach enhances the methodological rigor of the study by clearly outlining the scope of the review.

## 2. Biomaterials for additive manufacturing: classifications and functionalities

All manufacturing processes, including AM methods, require raw materials. These raw materials must be suitable for the properties of the parts to be manufactured [26–29]. AM technologies use a wide variety of materials tailored to the specific requirements of the application, such as mechanical properties, functionality and thermal resistance. Material types and manufacturing methods vary depending on the specific needs of the application. Each material class offers different advantages to AM processes, providing specific solutions in many areas of the industry [30–33]. Materials commonly used in the field of biomaterials have their own advantages and limitations. For example, polymers provide biocompatibility and flexibility, but may lack the mechanical strength required for certain load-bearing applications [34–38]. Metals like titanium alloys offer excellent strength and biocompatibility, making them suitable for implants, but can be costly and difficult to process. Ceramics are known as ideal materials for dental and orthopedic applications due to their high wear resistance and biocompatibility, but these materials can be quite brittle. Each of these materials has a wide range of applications [39–41], from medical devices to tissue engineering, and their advantages and limitations are carefully evaluated based on specific biomedical needs (table 1).

### 2.1. Polymer-based biomaterials

Polymeric materials are extensively applied in AM because of their favorable features, including biocompatibility, chemical adaptability, non-toxicity, biodegradability, and bioactivity. In this manuscript, the term ‘biopolymer’ refers specifically to natural polymers of biological origin, whereas ‘polymer’ without qualification denotes synthetic systems. The term ‘biodegradable’ is used to describe materials that can degrade under physiological conditions into non-

**Table 1.** Biomaterial classifications according to material categories [24, 25].

Type	Examples	Advantages	Disadvantages	Applications
Metals and alloys	<ul style="list-style-type: none"> <li>• Titanium,</li> <li>• Steel,</li> <li>• Chromium,</li> <li>• Gold,</li> <li>• Cobalt,</li> <li>• Platinum</li> </ul>	<ul style="list-style-type: none"> <li>• Easy to fabricate</li> <li>• High strength,</li> </ul>	<ul style="list-style-type: none"> <li>• Corrosive,</li> <li>• High elastic modulus,</li> <li>• Aseptic</li> <li>• Loosening,</li> </ul>	<ul style="list-style-type: none"> <li>• Orthopaedic implants,</li> <li>• Screws,</li> <li>• Pins,</li> <li>• Plate</li> </ul>
Polymers	<ul style="list-style-type: none"> <li>• Polymethyl methacrylate,</li> <li>• Polycaprolactone (PCL), polylactic acid (PLA),</li> <li>• Polycarbonates,</li> <li>• Polyurethanes</li> </ul>	<ul style="list-style-type: none"> <li>• Biodegradable,</li> <li>• Easily moulded,</li> <li>• Readily available,</li> <li>• Biocompatible,</li> <li>• Suitable mechanical properties</li> </ul>	<ul style="list-style-type: none"> <li>• Leachable in body fluids,</li> <li>• Hard to sterilise</li> </ul>	<ul style="list-style-type: none"> <li>• Orthopaedic and dental implants,</li> <li>• Prostheses, tissue engineering,</li> <li>• Drug delivery</li> </ul>
Natural biomaterials	<ul style="list-style-type: none"> <li>• Collagen,</li> <li>• Gelatine,</li> <li>• Fibrin,</li> <li>• Sodium alginate,</li> <li>• Chitosan,</li> <li>• Hyaluronic acid</li> </ul>	<ul style="list-style-type: none"> <li>• Similar biological activities,</li> <li>• Support cell migration,</li> <li>• Proliferation and differentiation</li> </ul>	<ul style="list-style-type: none"> <li>• Low yield,</li> <li>• Complex preparation</li> </ul>	<ul style="list-style-type: none"> <li>• Bioprinting of skin,</li> <li>• Multilayer complex skin structures</li> </ul>
Ceramics and carbon compounds	<ul style="list-style-type: none"> <li>• Calcium</li> <li>• Phosphate salts (HA),</li> <li>• Glass,</li> <li>• Aluminium/titanium oxides</li> </ul>	<ul style="list-style-type: none"> <li>• Biocompatibility</li> <li>• Corrosion resistance</li> </ul>	<ul style="list-style-type: none"> <li>• High modulus</li> </ul>	<ul style="list-style-type: none"> <li>• Dental implants,</li> <li>• Artificial hearing aids</li> </ul>
Composites	<ul style="list-style-type: none"> <li>• Dental fillings,</li> <li>• Carbon fibre reinforced methyl methacrylate cone cement,</li> <li>• Ultra-high molecular weight polyethylene</li> </ul>	<ul style="list-style-type: none"> <li>• Corrosive resistant</li> </ul>	<ul style="list-style-type: none"> <li>• Laborious manufacturing</li> </ul>	<ul style="list-style-type: none"> <li>• Dental fillings,</li> <li>• Rubber catheters and gloves.</li> </ul>

toxic byproducts. Biopolymers, which originate from renewable biological resources such as plants, animals, and microorganisms, have become increasingly valuable in biomedical contexts. They are now commonly employed in fields such as cardiac, bone, and hepatic regeneration, as well as in wound healing and drug delivery systems [42, 43]. A variety of natural and synthetic polymers and their corresponding biomedical applications are presented in table 2.

Natural biodegradable polymers are particularly versatile, with widespread use in tissue regeneration, gene therapy, controlled drug release, and related healthcare applications. However, despite their excellent biological activity and compatibility, they face several limitations, including low mechanical strength, high water solubility, instability of supply, potential immunogenicity, and denaturation during processing [44, 45].

By contrast, synthetic polymers such as poly-anhydrides, polyamides, poly- $\alpha$ -hydroxyesters, polyurethanes, and poly(ortho-esters) can generally be produced at lower cost than natural alternatives [46]. These materials are increasingly attractive in biomedical research because their molecular weight, chemical composition, and mechanical behavior can be tailored with precision. Although synthetic polymers inherently provide weaker support for cellular adhesion, targeted chemical modifications can be introduced to improve their ability to interact with living tissues [47].

Studies have shown that polymer-based biomaterials offer significant advantages in terms of biocompatibility and biodegradability. However, they appear to be more limited in terms of mechanical strength compared to metal and ceramic-based structures. This suggests that polymers alone may not be sufficient, particularly in load-bearing implant applications, and that they must be supplemented with composite materials.

## 2.2. Ceramics and metal-based biomaterials

Ceramics and metals are frequently used biomaterials in AM processes. Metal-based biomaterials are generally materials that include titanium, stainless steel, and cobalt-chromium alloys. These biometals have a more widespread use than bioceramics [64–66]. Metals have become indispensable for load-bearing parts due to their excellent mechanical properties and biocompatibility [67]. The ability to manipulate the microstructure of these metals with AM allows optimization of their mechanical performance, which is critical for applications in orthopedics and dental implants. Bioceramics are a type of material that is just beginning to develop in the AM sector due to their processing difficulties [68–70]. The melting points of ceramic materials are too high to melt under normal heating methods. Generally, attempts to process ceramics directly result in thermally induced cracks.

For this reason, indirect AM processing methods are used in ceramics. Indirect processing is achieved by combining ceramics with a polymeric binder and extrusion bioprinting or 3D powder printing. These bioceramics include tricalcium phosphate, hydroxyapatite, biphasic calcium phosphate, bioglass and polymer. Ceramics, especially calcium phosphate and hydroxyapatite, provide a biomechanical structure similar to bone tissue by forming bone-like structures. The best examples for the application of bioceramics are bones and teeth [71, 72]. The incorporation of bioceramics such as hydroxyapatite into AM processes is emphasized as a method to increase the osteoconductivity of scaffolds and promote bone regeneration [73]. Almost 70% of bone consists of ceramics, which are very close in chemical composition to calcium phosphate (CaP). Similarly, teeth also have a large CaP content. Some ceramic and metal-based biomaterials and their applications are shown in table 3.

Ceramic and metal-based structures stand out in clinical applications thanks to their high mechanical strength and biocompatibility. However, some studies in the literature report that porous structures increase cell adhesion and biointegration, while others report that excessive porosity negatively impacts mechanical integrity. These conflicting findings highlight the critical research challenge of porosity-strength in AM-fabricated implants.

## 2.3. Composite biomaterials

One of the newest material classes that has become prominent and widely used in AM methods in recent years is composite biomaterials. These biomaterials are formed by combining two or more materials with different properties. Composite biomaterials are usually composed of a combination of polymer, ceramic and metal components, thus providing both biocompatibility and mechanical strength [85]. Especially in the manufacture of polymer-based composites, the efficiency of the manufacture process is increased and the material strength is optimized by homogeneously distributing the additives added to the polymer matrix throughout the manufacture process and obtaining the desired mechanical properties. The raw material composition of biopolymer-based composites generally includes secondary phases such as matrix polymer, adhesive, plasticizer, surfactant and particles or fibers consisting of metal, ceramic or polymer composition. While adhesives increase the flexibility of the composite material; plasticizers improve rheological properties and facilitate the manufacture process. In addition, surfactants provide homogeneous dispersion of the secondary phase, thus improving the general properties of the composite material [86, 87].

Metal matrix composites produced with AM include particulate composites, fibrous composites,

**Table 2.** Biopolymer categories, associated AM techniques, and their biomedical applications.

Type	Biopolymer	AM technique	Applications	References
NATURAL	Cellulose	DIW, FDM, IJP	Neural, skin, tendons, muscle, cardiac, cartilage, and bone regeneration	[48, 49]
	Alginate	Extrusion (Nozzle-based)	Hollow vascular channels, bone, cartilage, neural, skin regeneration, and wound healing	[50]
	Gelatin	Extrusion, SLA	Aortic valves, neovascularization, cartilage, neural, bone, and skin regeneration	[51, 52]
	Chitosan	Extrusion, SLA	Gene delivery, wound dressing, bone, nervous, skin, liver, cardiovascular, and cartilage TE	[53]
	Collagen	Extrusion, IJP	Drug delivery, vascular, dental, cornea, bone, cartilage, and artificial skin regeneration	[54]
	SF (Silk Fibroin)	Microextrusion, SLA, IJP	Gene delivery, wound healing, hepatic, vascular, cornea, neural, tendon, bone, cartilage, and skin regeneration	[55, 56]
SYNTHETIC	PLA	Extrusion, SLA, IJP	Suture, neural, bone, skin cartilage, cardiovascular, ligament regeneration, and drug delivery applications	[57, 58]
	PVA (Polyvinyl Alcohol)	Extrusion, IJP	Drug delivery, wound dressing, bone, cartilage, and skin regeneration	[59]
	PGA (Polyglycolic Acid)	Extrusion, SLA, IJP	Surgical sutures, bone, ligament, and cartilage reconstruction	[60]
	PCL	Extrusion, SLA, IJP	Dentistry, vascular, bone, retina, skin regeneration, and pharmaceutical applications	[61, 62]
	PHB (Polyhydroxybutyrate)	Extrusion, IJP	Surgical implants, biomedical devices, bone, skin, cartilage regeneration, or breast augmentation	[63]

Note: In this study, extrusion-based methods correspond to nozzle-based techniques (e.g., FDM/FFF, DIW), while powder bed fusion methods correspond to laser-based techniques (e.g., SLM, SLS, EBM). Light-based methods (e.g., SLA, DLP) and inkjet printing (IJP)/binder jetting methods are presented as separate categories. This explanation ensures consistency between the terminology used in the text and the classification in the table.

FDM/FFF	Fused Deposition Modeling/Fused Filament Fabrication
DIW	Direct Ink Writing
SLM	Selective Laser Melting
SLS	Selective Laser Sintering
EBM	Electron Beam Melting
SLA	Stereolithography
DLP	Digital Light Processing
PBF	Powder Bed Fusion
LPBF	Laser Powder Bed Fusion
LPEF	Laser Powder Engineering Fabrication/Fusion
PEGDA	Poly(ethylene glycol) diacrylate
BG	Bioactive Glass
IJP	Inkjet Printing

**Table 3.** Overview of ceramic and metal biomaterials, their AM techniques, and their biomedical applications.

Type	Biomaterial	AM technique	Applications	References
Ceramic	Alumina, zirconia, Silicon Nitride, and Silicon Carbide	DLP	Bone scaffolds. Enhanced osteoconductivity through hydroxyapatite incorporation in scaffolds.	[74]
	Hydroxyapatite, Alumina, and Zirconia	PBF	Load-bearing implants. Bioinert ceramics provide structural support without adverse biological responses.	[75]
	Al-oxide	Binder Jetting, Vat polymerization	Osteosynthetic devices, bearing surfaces	[76, 77]
	Zirconium-oxide	SLS	Fixed partial dentures	[78]
	Tricalcium Phosphate, Hydroxyapatite, and Bioactive Glass	Material Extrusion	Tissue engineering. Development of bioceramic-based scaffolds with enhanced mechanical properties.	[73]
	Ti, Ti-Zr	SLM	Orthopedic implants. Optimized microstructure improves mechanical performance and biocompatibility.	[67]
Metal	Ti, Co-Cr, and 316L	EBM, LPBF, Extrusion, and Binder Jetting	Dental implants. Porous titanium structures facilitate bone ingrowth and vascularization.	[79]
	Ti, Ag and Cu	SLM	Custom implants. Integration of antimicrobial properties through silver and copper nanoparticles.	[80]
	Ti-6Al-4V	LPBF	Bone replacement. Unidirectional honeycomb structure.	[81]
	C-Cr-Mo alloys	EBM, and SLM	Orthopedic and dental implants	[82, 83]
	Ti-6Al-4V, Co-Cr, and Tantalum	SLM, EBM	Bone repair. Ability to create complex geometries that mimic natural bone architecture.	[84]

Abbreviations and classification terminology are consistent with those provided under table 2.

laminates, and functionally gradient materials (FGMs). These composite types provide advantages in terms of both design flexibility and material performance. Selective laser melting (SLM) and laser metal deposition (LMD) processes are the most preferred processes, especially for the use of metal matrix composites with AM [88]. The manufacture of ceramic matrix composites uses particles that are blended for homogeneity and then consolidated with SLS or another AM method, as in biopolymer composites. In addition, the binder spraying method is also used in the production of ceramic matrix composites. The binder spraying method provides dimensional accuracy and complex geometry in production; It allows the production of protrusions, arches and cellular structures due to the support of the powder bed [89–91]. The various types of composite biomaterials and their specific application areas are presented in detail in table 4. This table details the potential applications of each type of composite.

In addition to their diverse applications, composite biomaterials present both significant advantages and limitations in the context of additive manufacturing. Their advantages include the ability to tailor mechanical and biological properties simultaneously, for instance by combining the flexibility and biodegradability of polymers with the osteoconductivity and strength of ceramics (e.g., PCL/HA composites), or by introducing multifunctionality through polymer–metal systems (e.g., PLA/Fe<sub>3</sub>O<sub>4</sub> composites for magnetic guidance, drug delivery, and hyperthermia treatment). Nanocomposites reinforced with graphene or carbon nanotubes further enhance mechanical strength and bioactivity. However, these systems also face important challenges, such as difficulties in achieving homogeneous dispersion of phases, phase separation, and interfacial defects during processing, as well as limited long-term mechanical stability under cyclic loading. Moreover, the lack of standardized fabrication protocols and the scarcity of clinical validation remain critical barriers to translation. With ongoing advances in multi-material printing and surface functionalization, composite biomaterials are expected to play a central role in next-generation biomedical applications, provided that these challenges can be systematically addressed. Composite structures stand out for their potential to combine the advantages of different materials. However, the complexity of manufacturing parameters and the challenges of ensuring material compatibility indicate that there are still obstacles to overcome in transferring this approach to clinical applications.

### 3. Current innovations and translational case studies in biomedical additive manufacturing

AM is gaining increasing importance in bioengineering with its high precision and adaptability in

applications such as personalized prostheses, biocompatible implants and tissue engineering scaffolds. Recent developments in the field of biomaterials further advance the use of bioactive materials integrated with AM methods. In particular, materials such as biodegradable metals and elastin-based composites can be processed with AM to create temporary scaffolds that mimic natural tissues. These materials support cell growth, promote tissue regeneration and contribute to the formation of new tissue by dissolving in the body. In the future, it is anticipated that such materials with bioactive properties will be used more widely in bone and soft tissue engineering. Various case studies reveal the practical applications and success of AM technology in the biomedical field. For example, studies on the use of porous magnesium and iron scaffolds in bone tissue engineering show that these materials can support bone repair with their biocompatible and biodegradable properties. In addition, the use of hydrogel composites developed for tissue engineering with 3D printing techniques offers very promising results in areas such as organ replacement and wound healing. Such successful case studies pave the way for more widespread use of AM in biomedical applications. Recent research on biomaterial applications of AM methods highlights significant advances and diverse applications in various fields, especially in biomedical engineering. Recent studies have significantly advanced the understanding and application of biomaterials in AM, especially in the fields of tissue engineering and regenerative medicine (figure 1).

Overall, the case studies discussed in this section demonstrate both the opportunities and current challenges in transferring AM technologies to clinical practice. While some applications, such as dental implants and personalized prosthetics, have reached early clinical use, areas such as soft tissue regeneration or complex organ bioprinting are still largely experimental. This contrast highlights the need for interdisciplinary research to bridge the gap between laboratory-scale innovations and routine medical practice. These findings suggest that AM offers revolutionary potential in biomedical applications, but standardized manufacturing protocols and long-term biocompatibility studies are critical for its translation to clinical scale.

#### 3.1. Bone and tissue engineering

In recent years, advances in biomedical engineering have enabled the implementation of innovative approaches for bone and tissue regeneration. 3D bioprinting technology has developed groundbreaking solutions in regenerative medicine by offering personalized treatment options. This technology enables the production of biomimetic structures for bone and tissue engineering, the support of cellular activity and the acceleration of tissue healing

**Table 4.** Composite biomaterials, their AM techniques, and biomedical applications.

Type	Biomaterial	AM technique	Applications	Advantages	Limitations	References
Composites	PLA/CaCO <sub>3</sub> Composites	FDM	Surgical guides, orthoses, medical models and casts	Good biocompatibility, low cost, suitable for patient-specific guides	Brittle, limited mechanical strength	[92]
	PLA/Fe <sub>3</sub> O <sub>4</sub>	FDM	Tracheal stents. It is used to combat narrowing or collapse in the respiratory tract and to support the respiratory tract.	Magnetic guidance, multifunctionality	Risk of phase separation, limited clinical validation	[93]
	Alginate/glycerin	Extrusion	Skin dressing	Biocompatible, flexible, tunable degradation	Poor mechanical strength, sensitive to hydration	[94]
	PCL/Fe <sub>3</sub> O <sub>4</sub>	SLA	Tissue engineering. Magnetic guidance and targeted therapy.	Combines strength of PCL with magnetic responsiveness	Inhomogeneous dispersion, weak long-term stability	[95]
	PLA/Fe <sub>3</sub> O <sub>4</sub> /benzophenone	DIW	Cardiovascular implant. Biomedical devices.	Multifunctional (mechanical + magnetic + photocrosslinking)	Complex processing, limited scalability	[96]
	Gelatin/chitosan	Extrusion	Tissue engineering. Controlled drug release.	Natural origin, biodegradable, good drug loading capacity	Low mechanical strength, rapid degradation	[97]
	PCL/PEG	Extrusion	Bone, tissue engineering	Improved flexibility, hydrophilicity, cell adhesion	Reduced mechanical stability compared to pure PCL	[98]
	PEGDA	SLA	Bone, tissue engineering	High precision, tunable degradation properties	Limited mechanical strength, photoinitiator toxicity risk	[99]
	PLLA/PHBV	SLS	Bone tissue regeneration	Biocompatibility, slow degradation, osteoconductivity	Brittle nature, processing difficulties	[100]
	PCL/Fe <sub>3</sub> O <sub>4</sub> /BG	FDM	Bone regeneration. Treatment of hyperthermia. Local cancer drug release.	Synergistic antibacterial & magnetic effects, multifunctionality	Complex processing, risk of inhomogeneity	[101]
	Methacrylated alginate & Methacrylated HA	Extrusion	Tissue engineering: Deformation properties of hydrogels, transformation into artificial tissue structures in the biomedical field	Deformation control, good hydrogel-ceramic integration	Difficult reproducibility, weak mechanical load-bearing ability	[102]

Abbreviations and classification terminology are consistent with those provided under table 2.

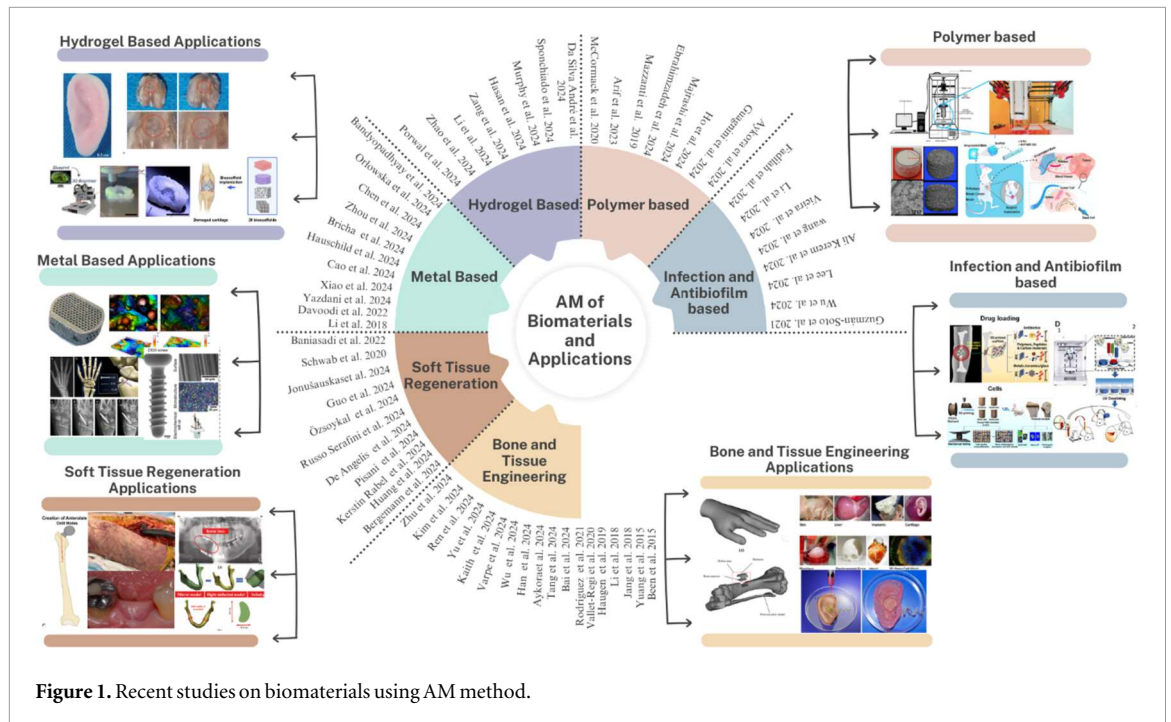


Figure 1. Recent studies on biomaterials using AM method.

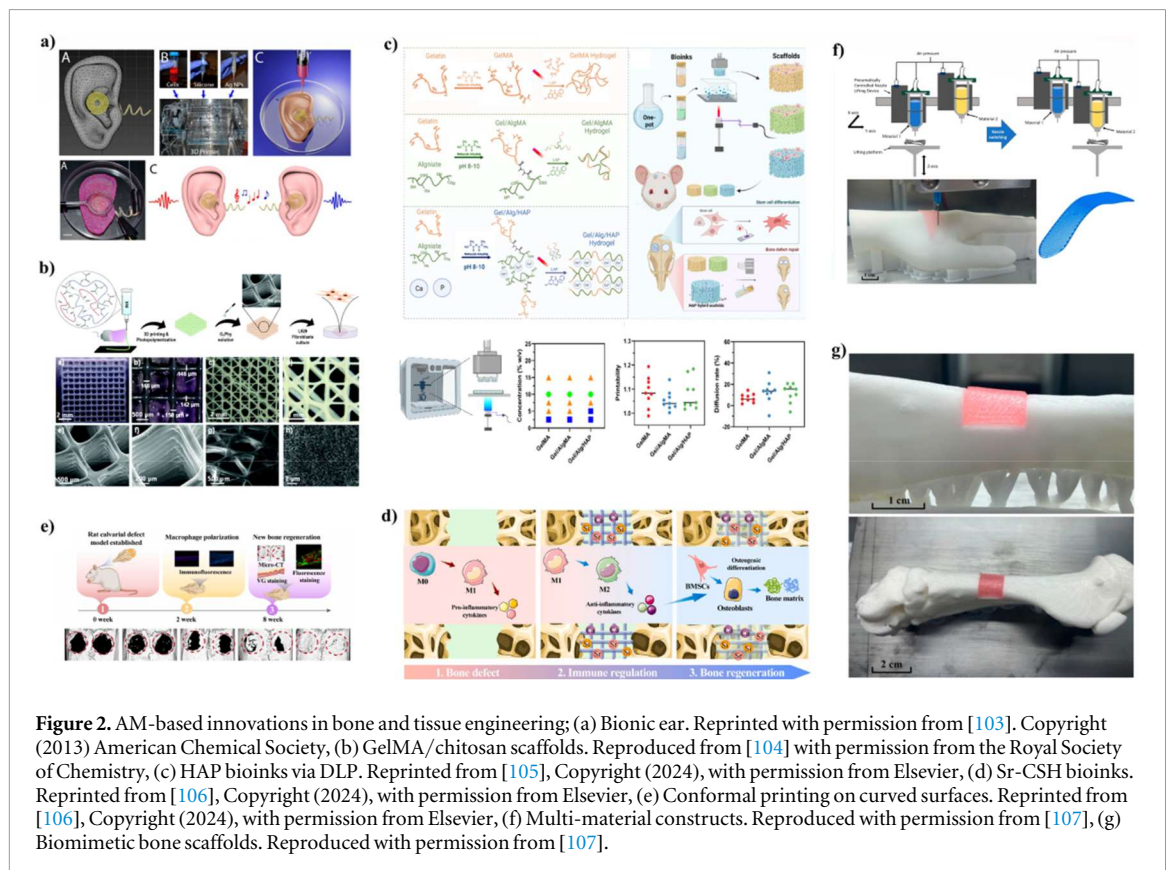


Figure 2. AM-based innovations in bone and tissue engineering; (a) Bionic ear. Reprinted with permission from [103]. Copyright (2013) American Chemical Society, (b) GelMA/chitosan scaffolds. Reproduced from [104] with permission from the Royal Society of Chemistry, (c) HAP bioinks via DLP. Reprinted from [105], Copyright (2024), with permission from Elsevier, (d) Sr-CSH bioinks. Reprinted from [106], Copyright (2024), with permission from Elsevier, (e) Conformal printing on curved surfaces. Reprinted from [106], Copyright (2024), with permission from Elsevier, (f) Multi-material constructs. Reproduced with permission from [107], (g) Biomimetic bone scaffolds. Reproduced with permission from [107].

processes. 3D bioprinting has been strengthened by a number of innovative approaches aimed at improving both material compatibility and functional performance. In this context, strategies that optimize the physical and biological properties of biomaterials play a critical role in the development of new treatment methods. In particular, the integration of 3D printing technology with biomimetic properties and studies

on advanced material properties have increased the potential in this field.

Innovative applications such as bionic 3D printed ear prototypes have provided precision engineering opportunities in regenerative medicine (figure 2). Mannoor *et al* [103] used 3D printing technology to produce a bionic ear that mimics the complex anatomical structure of the human ear and is integrated

with electronic components (figure 2(a)). In the study, a conductive antenna containing silver nanoparticles was combined with living chondrocyte cells embedded in an alginate-based hydrogel matrix and a three-dimensional bionic ear was created with the help of a CAD model. This structure combined both the biological properties of cartilage tissue and the electronic functions of an antenna capable of sensing electromagnetic signals. This bionic ear, grown in culture for 10 weeks, showed biological and mechanical improvements such as high cell viability (91.3%), proteoglycan accumulation and increased elastic modulus. It was also successfully tested as a functional bionic organ thanks to its ability to perceive stereo sounds. The study presents an innovative approach to the production of organs that exceed human biology in sensory and functional terms through the three-dimensional integration of biological tissues and nanoelectronic components.

Zhu *et al* [108] investigated strategies such as nanomaterials, growth factors, and immunomodulation methods to enhance the mechanical strength and improve the osteogenic capacity of Gelatin Methacryloyl (GelMA)-based bioinks used for bone regeneration. In the study, strategies such as nanomaterial additives (such as graphene oxide, nanoclay), growth factors (VEGF, BMP-2), and immunomodulation methods (M1 to M2 macrophage conversion) were applied. Experiments showed that nanomaterials increased the mechanical strength, growth factors promoted vascularization, and supported osteogenic differentiation in bioprinted structures. In particular, it was found that the biological activity of GelMA-based bioinks was significantly improved by functional additives, as was the mechanical strength equivalent to 3400 bar pressure. Mora-Boza *et al* [104] focused on the fabrication of multilayer 3D printing scaffolds using a two-step crosslinking technique with low-concentration GelMA/chitosan inks (figure 2(b)). In the study, the shape consistency of GelMA structures was increased by photopolymerization with ultraviolet (UV) light in the first stage, followed by ionic crosslinking with an innovative crosslinker, Glycerylphosphate (G1Phy). This approach enabled the fabrication of complex geometries and improved the mechanical strength and biological properties of the scaffolds. The structures could be printed without collapse up to 28 layers and showed long-term physiological stability. In cellular tests, G1Phy crosslinked scaffolds provided better cell adhesion, spreading, and proliferation than traditional TPP crosslinkers. This innovative technique holds promise for the fabrication of biocompatible, high-resolution, and stable 3D structures, especially for soft tissue engineering applications.

Kim *et al* [109] developed 3D printed constructs that promote osteogenic differentiation and accelerate bone healing by combining amorphous calcium magnesium phosphate (ACMP) bioceramics with

GelMA-based bioinks. In this study, the study included the synthesis of ACMP at different Ca/Mg ratios, evaluation of its cytocompatibility, and analysis of its osteogenic activity in co-culture with preosteoblast cells (MC3T3-E1). The printing compatibility and cell viability of GelMA/ACMP bioinks were investigated constructs containing 0.5% ACMP were found to best support osteogenic differentiation. The results showed that a controlled  $Mg^{2+}$  microenvironment is critical for early bone regeneration and ACMP may be a promising component in bone tissue engineering of 3D bioprinted constructs. Ren *et al* [105] developed hybrid bioinks containing hydroxyapatite and fabricated high-resolution structures using DLP technology using the 'one-pot synthesis' method (figure 2(c)). The study revealed that these bioinks provided superior bone regeneration by enhancing osteogenic differentiation. The study highlights the potential of these bioinks to be used in bone tissue engineering, which is a strong candidate for DLP 3D printing technology. Yu *et al* [106] combined immunomodulatory and osteogenic differentiation processes for the regeneration of critical-sized bone defects with strontium-doped xonotlite (Sr-CSH) and GelMA-based bioinks. The aim of the study was to design a bioink that modulates the immune response and promotes osteogenic differentiation, thereby improving both bone healing and impression sensitivity. *In vitro* analyses showed that Sr-CSH promoted the polarization of macrophages to the M2 phenotype and accelerated the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) (figure 2(d)). *In vivo* experiments, it was observed that GelMA-Sr-CSH bioink-imprinted scaffolds achieved almost complete bone regeneration in rat skull defects (figure 2(e)). This study highlights the potential of bioinks that provide both immunomodulatory and bone regeneration for the treatment of critical-sized bone defects.

Kaith *et al* [110] investigated the potential of polysaccharide-based bioinks such as alginate, chitosan and cellulose in tissue engineering and bone regeneration. The biomimetic properties of polysaccharides and controlled growth factor release were effective in creating complex anatomical structures. The study shows that polysaccharides are promising bioink components for tissue damage repair and treatment of bone injuries. Varpe *et al* [111] examined the applications of 3D bioprinting on human organs and highlighted the potential solutions offered by this technology in areas such as skin wound healing and bone defect repair. The review focused on the applications of bioprinting in skin wound healing, bone defect repair and aesthetic-reconstructive surgery. In addition, the material and method innovations in 3D bioprinting and the success of this technology in areas such as biocompatibility, vascularization and functional tissue formation were detailed. The study highlighted the importance of interdisciplinary collaboration for the transition of bioprinting to

clinical applications. Wu *et al* [112] investigated the role of the combination of 3D printing technology and nanotechnology in the development of innovative scaffolds that enhance vascularization for bone regeneration. The review focused on the use of different biomaterials such as calcium phosphate ceramics, polymers, and biocompatible metals and the ideal balance between mechanical strength and osteogenic potential. The study demonstrates the potential of 3D printed nanostructured scaffolds to enhance bone regeneration by promoting vascularization and highlights the great promise of these technologies for personalized medicine applications. The biological functionality of nanomaterials has enabled personalized medical solutions for bone healing.

Han *et al* [113] developed branched vascular scaffolds using high-precision 3D printing of plasticized PLCL elastomer. The aim of the study is to improve the controllability of microstructures of biocompatible and biodegradable thermoplastic elastomers, making their printing accuracy and mechanical properties closer to those of natural blood vessels. These structures have been shown to mimic natural vascular properties and are suitable for organ-on-a-chip applications. Aykora *et al* [114] emphasized that melatonin-loaded polymers support bone regeneration with their osteoinductive and anti-inflammatory properties when used in 3D bioprinting processes. The study emphasized that the osteoinductive, antioxidant and anti-inflammatory properties of melatonin can accelerate healing processes through controllable release in the treatment of large bone gaps. The research showed the potential of polymer-based bioinks to offer personalized solutions for bone regeneration and that melatonin supports angiogenesis, osteogenesis and immunomodulation processes in bone tissue formation. As a result, it was emphasized that melatonin-loaded bioprinted scaffolds offer a promising approach in the treatment of bone loss and that the challenges in the transition of this technology to clinical applications must be overcome. Tang *et al* [107] developed a conformal 3D printing algorithm that enables *in situ* repair applications on free-form surfaces. The aim of the study is to overcome the limitations of traditional 3D printing and enable precise printing on curved and free-form surfaces (figure 2(f)). The developed algorithm uses vector projection and coordinate transformations to plan the printing motion paths. In experiments conducted on human hand and porcine tibia models, it was shown that conformal printing can repair both skin and bone defects with high accuracy (figure 2(g)). The obtained results support the usability of this technology in tissue engineering and personalized medicine applications and emphasize that it is an important step towards clinical applications. Thus, the potential to repair tissue and bone defects with high precision was demonstrated. Kim *et al* [115] developed a lipoplex-loaded 3D bioprinted bilayer scaffold to

optimize the controlled release of bone morphogenetic protein 2 (BMP2) and reduce the risk of heterotopic ossification. The results showed that this system reduces the risk of heterotopic ossification by increasing the local concentration of BMP2, providing a promising bioengineering solution for bone regeneration. Bai *et al* [116] discussed the osteogenic functions of bioactive materials used in bone tissue engineering and the development of these materials with integrated strategies. The study highlights that biomaterials support the formation of new bone tissue by enhancing cellular adhesion, proliferation, and osteogenic differentiation. The review discussed how innovative approaches such as 3D bioprinting technologies and physical stimuli-responsive strategies are used to produce multifunctional biomaterials with integrated therapeutic and regenerative properties. In addition, the effect of biomaterials that promote stem cell differentiation on osteogenesis and the potential molecular pathways involved in this process are detailed. The study highlights the opportunities and challenges in the development of innovative materials that can be used in bone regeneration. Haugen *et al* [117] discuss ideal biomaterials for bone grafts, emphasizing the limitations of traditional allografts and demineralized bone matrix products due to high costs and insufficient clinical data. They highlight the potential of new bioactive glass (BG) substitutes produced by advanced methods such as 3D printing that could address these issues by enabling mass production and customization. Li *et al* [118] investigated additively produced biodegradable porous magnesium, demonstrating its potential as a scaffold material due to its biocompatibility and ability to support cell growth. Their findings suggest that magnesium scaffolds can degrade in physiological environments and provide a temporary support structure that can be replaced with natural bone over time.

Rodríguez-Cabello *et al* [119] focused on the development of elastin-based fibrous scaffolds that can mimic the extracellular matrix (ECM) in tissue engineering. In their study, they discuss the potential of elastin to integrate biomechanical and biomolecular cues into scaffold design and demonstrate the versatility of this material in creating biocompatible and functional biomaterials. They particularly emphasize the use of advanced polymer processing technologies, such as electrospinning and AM, in the production of elastin-based nanofibers, indicating that elastin-based structures are an important candidate for future 3D bioprinting and personalized implant design. Therefore, this study contributes directly not only to elastin biology but also to the development of AM-based biomaterial manufacturing strategies. Yuan *et al* [120] studied a robocasting method to create porous  $\beta$ -TCP (Tricalcium phosphate) scaffolds for the release of anti-tuberculosis drugs. They used  $\beta$ -TCP, paraffin and other additives

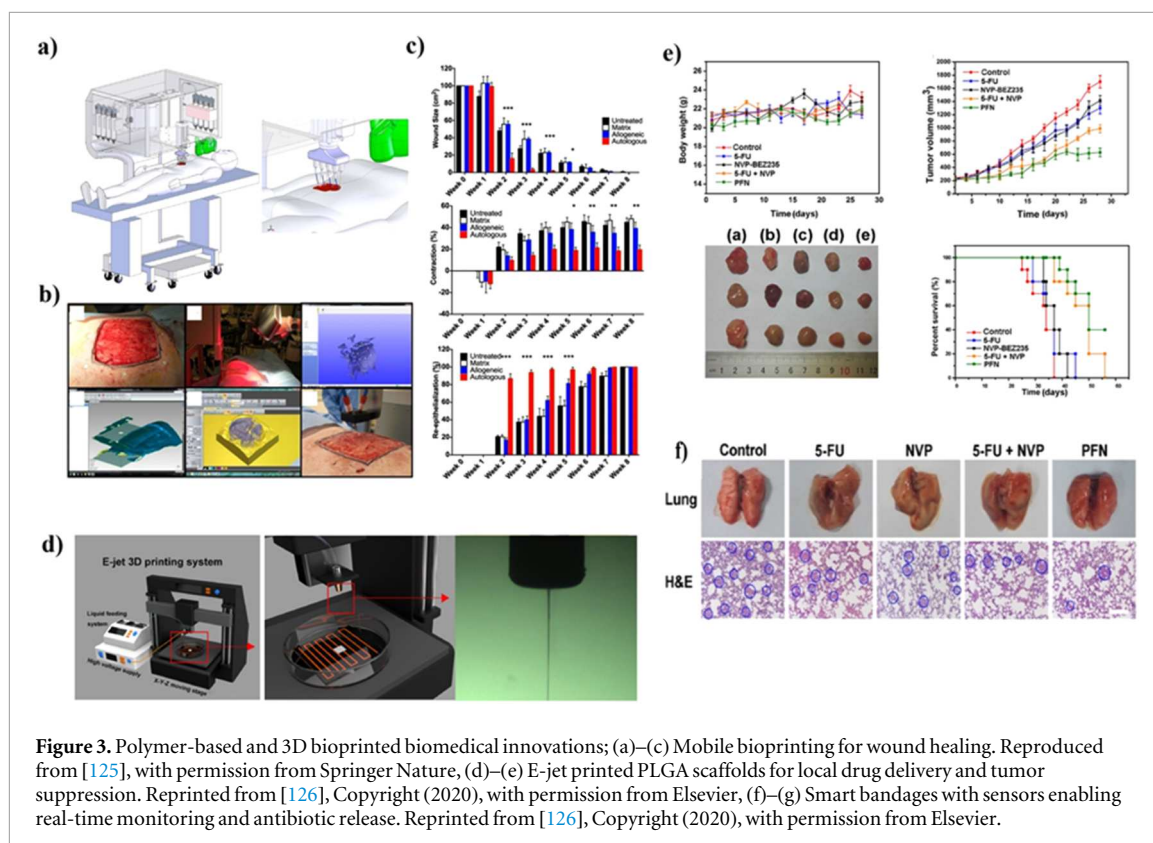
as ink for printing. Then, the porous  $\beta$ -TCP scaffolds were sintered at 1100 °C for 2 h to remove paraffin and densify the scaffold. Anti-tuberculosis drugs, rifampin (RFP) and isoniazid (INH), were loaded into porous  $\beta$ -TCP (Tricalcium phosphate) scaffolds with PLGA by different centrifugation steps. They determined the total porosity of the sintered scaffolds as  $61.76 \pm 2.53\%$ , 400  $\mu\text{m}$  macroporosity as  $42.5 \pm 1.23\%$  and 2–8  $\mu\text{m}$  microporosity as  $19.26 \pm 2.33\%$ . They observed that the maximum compressive strength of such scaffolds was  $3.31 \pm 0.64$  MPa. Vallet-Regí *et al* [121] comprehensively reviewed biomaterials that can be used to combat bone infections, focusing specifically on antimicrobial coatings, surface modifications, nanocarrier systems, and 3D-printed antibacterial scaffolds. The study states that antibacterial agents and biocompatible coatings that can be integrated onto implant surfaces are critical for reducing the risk of infection in orthopedic surgeries. Furthermore, it emphasizes the transformative potential of rapid prototyping and bioplotter-based AM techniques in the production of multifunctional scaffolds that can simultaneously provide antibacterial activity and bone regeneration. In this context, the article sheds light not only on biomaterial selection but also on how AM technologies can be effectively used in the design of future personalized orthopedic implants. Been *et al* [122] investigated the use of PCL scaffolds to promote bone healing in human tooth extraction sockets. In this context, PCL scaffolds fabricated using a FDM-based 3D printing technique were placed in the tooth extraction cavity without any filling material, and bone regeneration was evaluated after six months of follow-up. The study findings demonstrate that 3D-printed biodegradable PCL scaffolds significantly contribute to the maintenance of alveolar crest height and bone tissue regeneration. These results represent a significant step not only in dental implantology but also in the translation of AM-based biomaterials into clinical applications for personalized and functional bone regeneration.

### 3.2. Hydrogels and polymer-based materials

Hydrogels and polymer-based materials play a critical role in the fields of tissue engineering, regenerative medicine, and controlled drug release, as one of the indispensable components of biomedical engineering. These materials are used in various applications such as tissue regeneration, wound healing, and biomedical implant design thanks to their capacity to mimic the physical, mechanical, and biochemical properties of natural tissues. While polymer-based hydrogels can be shaped specifically for biomedical applications with their properties such as high water content, biocompatibility, and biodegradability, the possibilities provided by 3D bioprinting technologies make it possible to use these materials in the creation of more complex and functional structures. In recent

years, polymer-based hydrogel systems have focused on improving biomimetic properties, increasing mechanical strength, and optimizing cellular integration. Modifying hydrogels with magnetic nanoparticles, bioactive glasses, or biologically active molecules increases the biomedical potential of these materials. In addition, 3D printing methods that enable personalized medicine applications offer innovative solutions in the process of producing complex tissue structures. In this context, various case studies focusing on the advances in biomedical engineering of hydrogels and polymer-based applications have been discussed.

In the literature, Majrashi *et al* [123] examined the impact of advanced 3D printing technologies on polymer-based drug delivery systems. The study emphasizes that 3D printing plays a revolutionary role in drug delivery systems, offering new possibilities in personalized medicine, controlled drug release, and the production of complex formulations. Starting from the historical development of 3D printing, the research examined different applications of this technology in pharmaceutical production. Different 3D printing methods (FDM, SLA, SLS, inkjet printing) and how these methods are used in the production of drugs (tablets, capsules, implants, films, patches) were discussed. The study also evaluated how materials such as hydrogels, aerogels, and biocomposites were used in 3D printing-supported drug delivery systems. The results showed that 3D printing can precisely control drug release kinetics, dosing, and formulation design. However, the study also highlighted current obstacles such as regulatory challenges, scalability issues, and material compatibility, and stated that solving these issues is an important focus for future research. Ho *et al* [124] comprehensively evaluated the potential of natural polymers such as silk, collagen, gelatin, elastin, cellulose, chitosan, alginate, and hyaluronic acid in wound healing applications. The study emphasizes that these biopolymers, thanks to their biocompatible, biodegradable, and safe structures, can be integrated into traditional and modern treatment strategies and have yielded positive clinical and preclinical results. Most notably, these natural polymers are being used not only in conventional dressings but also in next-generation wound therapies through 3D bioprinting and intelligent stimuli-responsive material designs. In particular, material format and morphology have been shown to directly impact the wound healing process; in diabetic ulcer and full-layer wound models, 3D-printed chitosan, gelatin, and cellulose-based scaffolds have been shown to accelerate granulation tissue formation, vascularization, and epithelialization. In this respect, the study reveals not only the importance of natural polymers in existing products, but also their strategic role that will shape the future of AM-based personalized wound management solutions.



Albanna *et al* [125] developed an innovative mobile bioprinting system to accelerate the healing of large, full-thickness skin wounds. The aim of the study was to accelerate skin regeneration and minimize scar formation by directly layering autologous dermal fibroblasts and epidermal keratinocytes into the wound. In their study, autologous cells (dermal fibroblasts and epidermal keratinocytes) were combined with fibrinogen and collagen-based hydrogel and printed onto the wound. The system consists of an integrated 3D scanner and a layered printing nozzle mechanism to determine the topography of the wounds (figure 3(a)). They created 3×2.5 cm full-thickness skin excision wounds on mouse models. They tested autologous cell printing by creating four full-thickness wounds of 10×10 cm in pig models (figure 3(b)). As a result of the study, they found that bioprinted wounds closed completely within 3 weeks, while this period was 5 weeks in the control groups. They also observed organized dermis and keratinized epidermis in the sixth week in bioprinted wounds. New epithelial layer was formed in the second week with bioprinted autologous cell treatment. The contraction rate was found to be 50% lower in bioprinted wounds (figure 3(c)). CD31 positive mature blood vessels were formed in the fourth week, which supported tissue maturation. Masson's Trichrome staining confirmed the formation of mature dermis with large and organized collagen fibers in bioprinted wounds. Bioprinting showed faster re-epithelialization and layered structure formation compared to existing cell spraying technology. As a result, the

mobile bioprinting system accelerated wound healing and reduced scar formation by enabling the rapid and layered application of autologous skin cells to the wound. Especially in large surface wounds, this technology provides significant progress by offering personalized treatment opportunities.

Zhao *et al* [127] developed a layer-by-layer (LBL) self-assembly method to improve the mechanical properties and cytocompatibility of ODMA-GelMA hydrogels used in 3D bioprinting. In the study, a multilayer composite membrane was formed by applying silk fibroin (RSF) and chitosan (CHI) layers to the surface of GelMA containing dopamine methacrylamide (ODMA) via electrostatic interactions. This approach significantly increased the compressive strength and Young's modulus of ODMA-GelMA hydrogels, and 10-layer structures were found to be the most ideal structure supporting both mechanical performance and cell proliferation. *In vivo* and *in vitro* tests revealed that these hydrogels exhibited low toxicity and high biocompatibility. The study highlights the potential of the developed ODMA-GelMA structures in tissue engineering and artificial organ applications. Ebrahimzadeh *et al* [128] investigated the use of magnetic nanoparticles (MNPs) containing iron (II, III) oxide (Fe<sub>2</sub>O<sub>3</sub> and Fe<sub>3</sub>O<sub>4</sub>) in polymer-based 3D bioprinted scaffolds for bone tissue engineering. The study investigates the potential of these magnetic materials to accelerate bone regeneration by enhancing osteoconductivity, osteoinductivity and angiogenesis properties. In this study, conventional (electrospinning, freeze-drying) and advanced (3D

printing) methods used for the preparation of magnetic scaffolds are detailed. The combination of MNPs with materials such as PCL, PLGA and hydroxyapatite was investigated to optimize properties such as biocompatibility and biodegradability in the skeletal system. In addition, the role played by magnetic fields in bone tissue formation by enhancing cellular activity was emphasized. The results showed that magnetic scaffolds not only increased cellular adhesion and proliferation, but also optimized properties such as controlled drug release and mechanical stability. The study highlights the clinical potential of magnetic scaffolds in biomedical applications.

Yang *et al* [126] developed implantable PLGA scaffolds containing 5-Fluorouracil (5-FU) and NVP-BEZ235 using E-jet 3D printing technology (figure 3(d)). The aim of the study was to suppress breast tumor growth and reduce lung metastasis through local drug delivery. Compared to traditional chemotherapies, these implants offer the advantages of controlled drug delivery and low systemic toxicity. In their study, the combination of 5-FU and NVP-BEZ235 using PLGA polymer was integrated into porous scaffolds by E-jet 3D printing. The pore sizes were set as 50, 100, 150, and 200  $\mu\text{m}$ . The controlled release profiles of 5-FU and NVP-BEZ235 were investigated in PBS medium. The antitumor effect of drug-loaded scaffolds was evaluated using MDA-MB-231 breast cancer cells. An orthotopic breast tumor model was established using MDA-MB-231 cells in BALB/c nude mice. PFN scaffolds were surgically implanted into the tumor site. They were compared with 5-FU, NVP-BEZ235 and the combination of the two drugs via systemic injection. As a result of the study, 5-FU and NVP-BEZ235 from PLGA scaffolds showed rapid release for the first 7 days, followed by slow and prolonged release phases. The release rate increased as the pore sizes increased. PFN scaffolds increased the apoptosis rate in MDA-MB-231 cells to 37.83%, which was significantly higher than the free drug groups. MTT analysis and fluorescence imaging results showed that the PFN scaffold group reduced cell viability the most. The implantation of PFN scaffolds reduced the tumor volume by more than 60% at the end of 4 weeks (figure 3(e)). PFN scaffolds significantly reduced the number of metastatic foci and were superior to systemic injections. H&E staining showed tumor necrosis and fewer metastatic foci in the PFN scaffold group (figure 3(f)). It was determined that PFN scaffolds did not show toxicity to blood cells and the hemolysis rate was at a safe level of 1.21%. No toxicity was found in liver, spleen, kidney and heart tissues. This study demonstrated that drug-loaded PLGA scaffolds prepared by E-jet 3D printing method were effective in localized drug delivery. PFN scaffolds provided superior results compared to systemic drug injections in both suppressing tumor growth and reducing metastasis.

Bhatt *et al* [129] have developed hydrogel-based scaffolds and 3D bioprinting technologies for use in liver tissue engineering. The aim of the study is to provide innovative solutions for the treatment of liver failure and diseases by increasing the natural regenerative capacity of liver tissue. In the study, biocompatibility, biodegradability and mechanical strength properties of scaffolds produced from natural polymers such as collagen, alginate and gelatin and synthetic polymers such as PLGA and PEG were evaluated. Nano-hydrogel structures supported the differentiation and proliferation of hepatocytes thanks to their high surface area and biomimetic microenvironment. Patient-specific, complex liver tissue models were produced using 3D bioprinting methods (extrusion, inkjet, light curing). *In vitro* experiments have shown that these structures support cellular integration and liver functions. However, it has been stated that obstacles such as immune responses and long-term stability need to be resolved in clinical applications. The results suggest that these scaffolds and bioprinted structures are a promising tool in liver tissue-on-a-chip technologies for treating liver diseases and for drug testing. Guagnini *et al* [130] developed a new composite material for bone tissue engineering by adding biological glass, called BGMS10, to alginate and hydroxyapatite (HAp)-based scaffolds. The scaffolds were produced using the freeze-drying method and are not a direct application of AM. However, the BGMS10 additive's enhancement of osteogenic activity, mechanical strength, and antibacterial effects due to the release of strontium and magnesium ions suggest that this material could be an important reference in the design of bone tissue scaffolds produced through AM in the future. Aykora *et al* [114] investigated the use of melatonin (Mel) loaded polymers in bone tissue engineering with 3D bioprinting techniques. The aim of the study is to provide an effective solution for the treatment of large bone losses by using the antioxidant, anti-inflammatory and osteoinductive properties of melatonin. The study examined the combination of natural and synthetic polymers with Mel to obtain materials suitable for bioprinting. It was stated that polymers such as PLGA, PCL and alginate in particular provide controlled drug release thanks to their biocompatibility and biodegradability properties. The study showed that Mel loaded polymers promote osteoblast proliferation, VEGF production and cellular differentiation. The results revealed that scaffolds produced via 3D bioprinting can offer personalized treatment options in tissue engineering and accelerate bone regeneration with the slow release of Mel. This study provides a comprehensive review supporting the osteogenic effects of Mel loaded polymers in both *in vitro* and *in vivo* models.

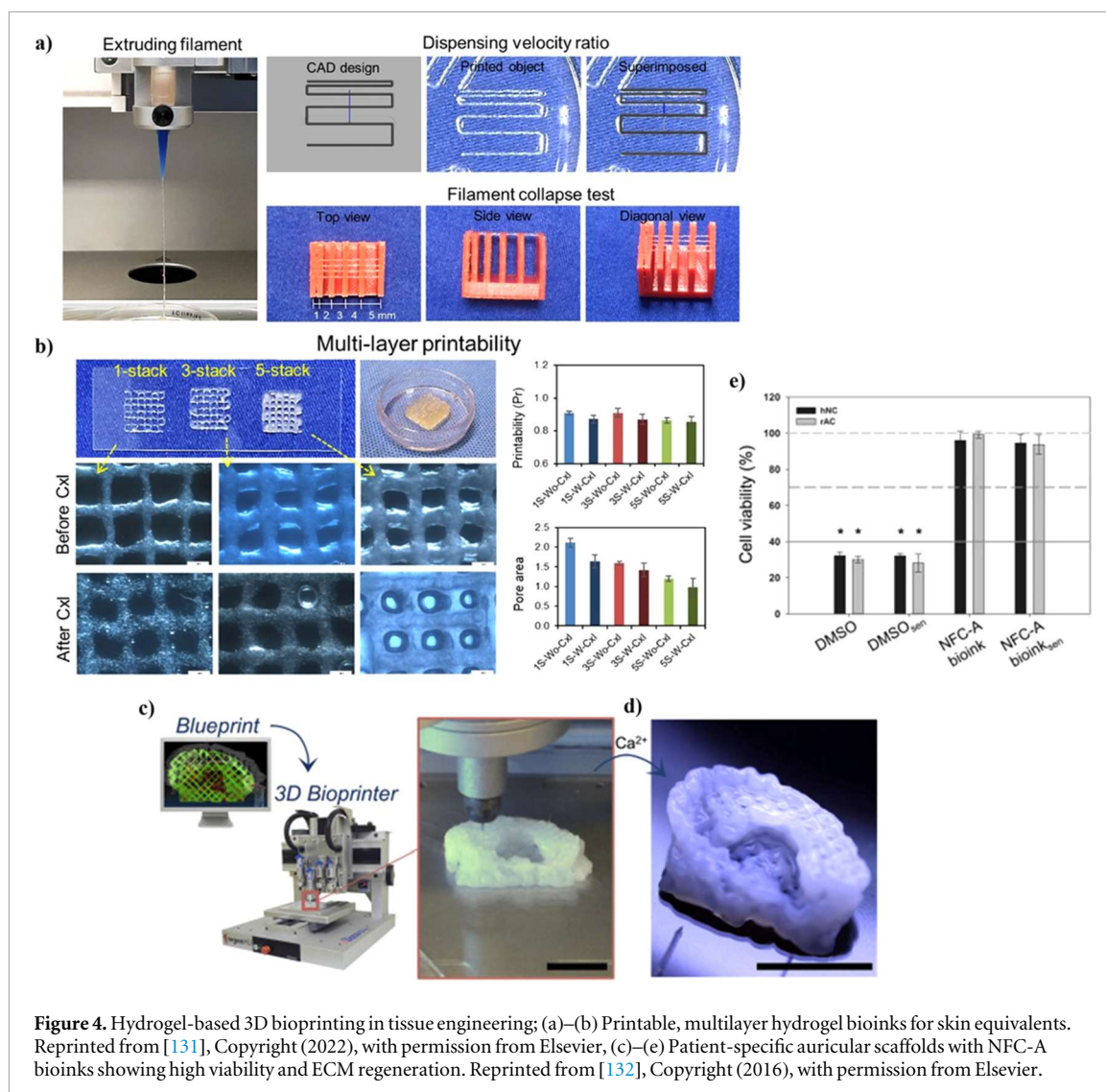
Porwal *et al* [133] have extensively reviewed the potential of hydrogel-based 3D printing formulations for tissue engineering in terms of sustainability and

innovative approaches. The study highlighted that hydrogel-based 3D printing offers new possibilities for tissue regeneration, personalized therapies, and biomedical applications with biomaterials and bioprinting technologies. The review discussed the advances in hydrogel compositions and their implications for applications such as different tissues, wound healing, and smart biomaterials. It also highlighted the challenges faced in hydrogel-based tissue engineering such as improving mechanical properties and overcoming regulatory hurdles. The study highlights that hydrogel-based 3D printing has the potential to revolutionize tissue engineering, but the need for innovation and improvement in this area continues. Da Silva André *et al* [134] adapted and optimized existing protocols to improve protein isolation from three-dimensional hydrogel scaffolds based on polyethylene glycol (PEG), collagen, and alginate. These methods, supported by TRIzol™-based lysis and phase separation techniques, were customized to the physical and chemical properties of different hydrogel types and aimed to achieve higher yields and quality. While the direct focus of the study was protein analysis, it is noteworthy that the hydrogel scaffolds used are bioink components commonly used in bioprinting applications. Therefore, the developed isolation protocols can be considered a critical tool not only for cell biology and tissue engineering research but also for the functional analysis of cytoskeletal systems obtained from AM-based 3D bioprinting. Thus, the study provides a significant methodological contribution to the understanding of biomaterial-biology integration and the biological validation of AM-produced hydrogel structures.

Rashmi Ramakrishnan *et al* [131] have developed an innovative bioink consisting of alginate-gelatin-diethylaminoethyl cellulose-fibrinogen (ALG-GEL-DCEL-FIB) components for use with 3D bioprinters for skin tissue engineering. The aim of the study was to optimize a bioink system that supports cell viability, is biocompatible, provides long-term stability, and can create skin tissue equivalents. In their study, alginate and gelatin-based bioink was supported with DCEL and fibrinogen to form a cross-linked hydrogel structure (figure 4(a)). This combination provided biocompatibility (gelatin and fibrinogen) and structural stability (alginate and DCEL), supporting the formation of dermal and epidermal layers. Using the bioprinter (RegenHu 3D Discovery), dermal layers containing fibroblasts (6 layers) and epidermal layers containing keratinocytes (2 layers) were printed. The bioink was carefully mixed to ensure even distribution of cells and placed in the printer cartridges (figure 4(b)). As a result of the study, Bioink was found to be successful in terms of printability with smooth filament formation and excellent shape fidelity. The multilayered structures maintained their stability even after printing, and the line spacing (1.5 mm) was maintained properly. Micro-CT analysis

showed that the bioprinted structures contained a highly connected and homogeneous pore network. The hydrogel provided an ideal moist environment for skin tissue regeneration with a water absorption of  $49.8 \pm 3.3\%$  and a swelling ratio of  $1.99 \pm 0.13$ . ALG-GEL-DCEL-FIB hydrogel was found suitable for dermal and epidermal applications with an elastic modulus of  $96.09 \pm 11.10$  kPa. At the end of 21 days of culture, 1.5-fold proliferation of fibroblasts and 3-3.5-fold proliferation of keratinocytes was observed. Strong expression of CK14 (epidermal) and collagen type-I (dermal) markers confirmed the biomimetic properties of the tissue. Epidermal and dermal gene expression was observed to be significantly higher in 3D cultures compared to 2D cultures. This study proved that ALG-GEL-DCEL-FIB bioink formulation is an effective option for 3D bioprinters. Printed structures exhibited biomimetic properties for the creation of skin tissue equivalents and supported cell proliferation. In addition, the long-term stability, controlled degradation and cost-effectiveness of the bioink suggest that it offers a promising solution for wound healing applications.

Zhang *et al* [135] investigated the potential of hydrogel-based 3D bioprinting technology for joint cartilage regenerative engineering. The study draws attention to the limited self-renewal capacity of cartilage tissue due to its avascular structure and the increasing prevalence of degenerative joint diseases such as osteoarthritis. It was emphasized that traditional treatments are inadequate in cartilage regeneration, and the role of 3D bioprinting in eliminating these deficiencies was highlighted. The study examined the use of natural and synthetic hydrogels as bioinks, the biocompatibility and mechanical properties of these materials in detail. In addition, it was stated that thanks to bioprinted structures, cellular distribution can be precisely controlled, biochemical and biomechanical properties can be regulated, and natural cartilage tissue properties can be imitated. In addition, it was stated that bioprinting processes can accelerate the integration process into clinical applications with their high sensitivity, designable pore structure, and low immunological rejection. Murphy *et al* [136] developed a hydrogel suitable for 3D printing containing gelatin methacryloyl (GelMA), chondroitin sulfate (CS), and hyaluronic acid (HA) for tissue engineering applications. The study conducted extrusion-based 3D printing experiments of these biomimetic hydrogels and evaluated their shape-maintaining properties. Furthermore, a freeze-drying technique was used to create porous scaffolds that support cell proliferation. In a study examining mechanical, rheological, and swelling behaviors, the combined use of HA and CS increased the swelling rate of the hydrogel and improved its mechanical strength. Cell culture tests revealed high fibroblast viability and proliferation. These results demonstrate that GelMA/CS/HA hydrogels are promising for



**Figure 4.** Hydrogel-based 3D bioprinting in tissue engineering; (a)–(b) Printable, multilayer hydrogel bioinks for skin equivalents. Reprinted from [131], Copyright (2022), with permission from Elsevier. (c)–(e) Patient-specific auricular scaffolds with NFC-A bioinks showing high viability and ECM regeneration. Reprinted from [132], Copyright (2016), with permission from Elsevier.

tissue engineering and implant technologies in terms of both processability and biocompatibility through 3D printing. Martínez Ávila *et al* [132] developed a nanocellulose-alginate (NFC-A)-based bioink containing human nasal chondrocytes for auricular cartilage tissue engineering (TE) (figure 4(c)). The study aimed to create patient-specific cartilage constructs using 3D bioprinting technology for the correction of traumatic or congenital auricular deformities. The study evaluated the printability, cellular compatibility and resynthesis of cartilage ECM (external cell matrix) components of NFC-A bioink. In their study, NFC-A bioink, consisting of a mixture of nanofibrillar cellulose (NFC) and alginate, was optimized to provide both biocompatibility and high viscosity. Human nasal chondrocytes (hNC) were homogeneously distributed in NFC-A bioink. Auricular constructs were printed based on models generated by magnetic resonance imaging (MRI) of the human ear. Chondrocytes were loaded into NFC-A hydrogels to form open-pore 3D structures (figure 4(d)). Cell viability, biocompatibility and resynthesis of cartilage ECM components were analyzed during 28 days of culture.

Sulfated glycosaminoglycan (s-GAG), collagen Type II, aggrecan and other ECM proteins were evaluated. As a result of the study, NFC-A bioink allowed the printing of auricular structures and open-pore cellular structures with high shape fidelity. The structures maintained their stability and did not deform during 28 days of culture. Chondrocyte viability in NFC-A bioink remained high (over 70%) even after printing (figure 4(e)). Chondrocyte proliferation increased during the culture period. A significant increase was observed in cartilage-specific genes such as SOX9, COL2A1 and ACAN. Collagen Type II and aggrecan were densely accumulated around the cells. At the end of 28 days, GAG accumulation was two-fold compared to the first 14 days of culture. Alcian blue staining showed a homogeneous distribution of s-GAG in the ECM. The cells maintained the cartilage phenotype, exhibiting round and regular morphology. This study demonstrates that NFC-A bioink offers a promising platform for auricular cartilage regeneration. Patient-specific auricular constructs allowed both high printing fidelity and cartilage-specific ECM resynthesis.

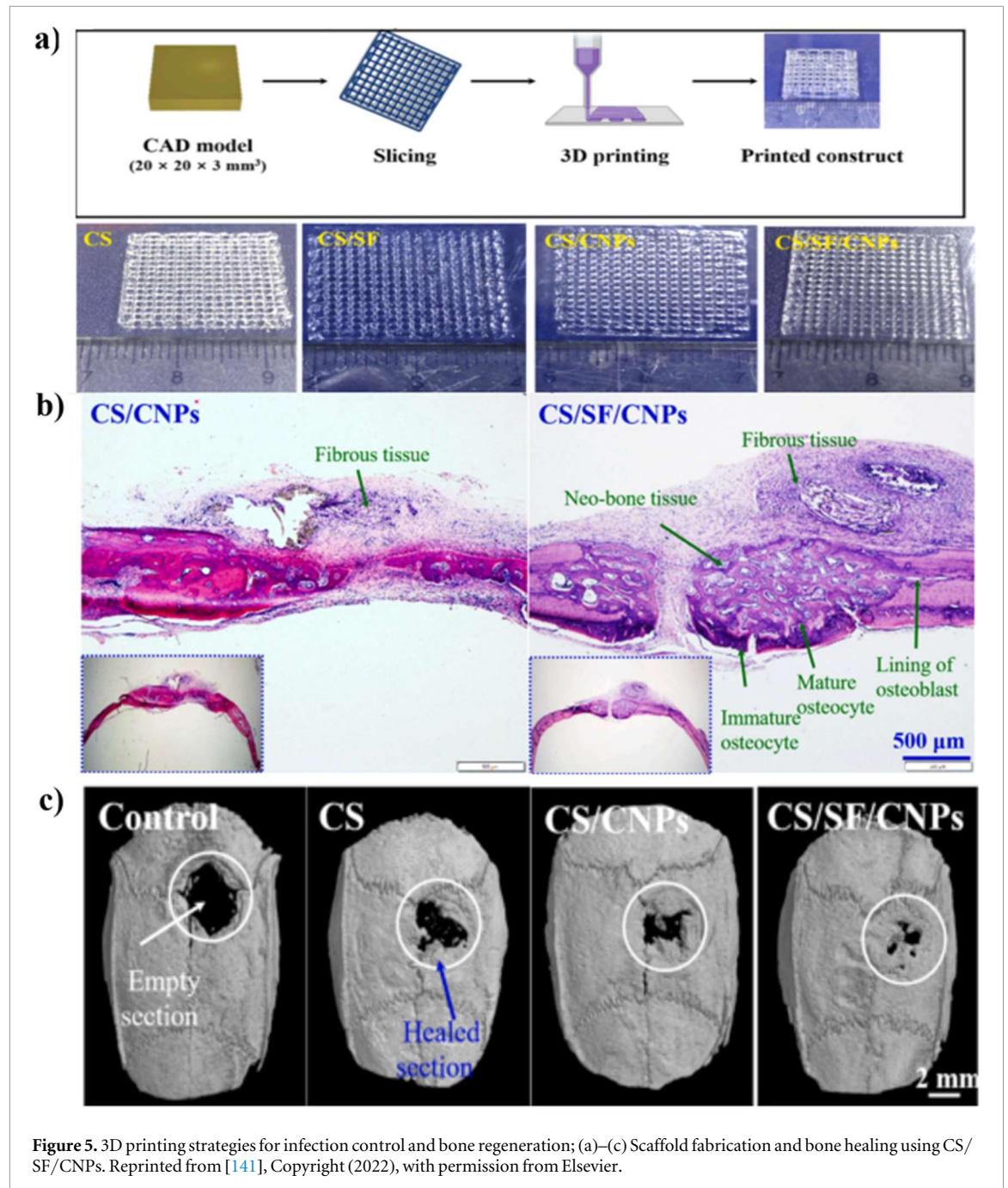
Sponchiado *et al* [137] modified potato starch for 3D printing of bone bioscaffolds using a 'clean' method called dry heat treatment (DHT) to improve hydrogel performance. The study investigated the effects of 1, 2, and 4 h of DHT treatment at 130°C on the structural and physicochemical properties of starch. The results showed that DHT partially depolymerized starch molecules by the formation of carbonyl groups, and these changes increased the properties such as strength, storage modulus, and printing accuracy of the hydrogels. Bioscaffolds obtained from starches modified with DHT exhibited lower biodegradability, decreased swelling strength, and improved mechanical performance compared to native starch. In particular, 1 h of DHT treatment at 130 °C provided the best results. These findings indicated that DHT-modified potato starch is a promising biomaterial for 3D printing in biomedical applications. Jang *et al* [138] provide a comprehensive overview of hydrogel composite 3D printing techniques, including laser-based, nozzle-based, and inkjet printing systems. They divide hydrogel composites into four main types: polymer-hydrogel, particle-reinforced, fiber-reinforced, and anisotropic filler-reinforced systems. The review discusses the potential applications of these composites in tissue engineering, highlighting the ongoing challenges in optimizing their mechanical properties and biocompatibility for clinical use. Mazzanti *et al* [139] review the mechanical properties of polymers containing natural fillers when processed via FDM. Their findings suggest that incorporating natural fillers can improve the mechanical performance of 3D printed materials, making them more suitable for biomedical applications. The review highlights the need for further research to optimize processing parameters and material formulations. McCormack *et al* [140] investigate the use of suspension baths in 3D bioprinting, which allows for the printing of polymer-rich structures. This method can increase the viability of encapsulated cells and improve tissue development, indicating a promising direction for bioprinting Technologies.

### 3.3. Infection and antibiofilm

Infection control and antibiofilm applications are of great importance in critical areas of biomedical engineering, especially in implant technologies, wound healing and development of medical devices. The ability of microorganisms to form biofilms complicates traditional treatment methods and complicates the management of infections. In this context, 3D printing technologies enable the design of customized surfaces, coatings and biomaterials for infection control and antibiofilm solutions, enabling new generation therapeutic approaches. In recent years, innovative biomaterials that both suppress infection and support tissue regeneration have been developed by integrating antibacterial agents and biologically

active components into polymer-based systems. 3D printed coatings and scaffolds are used to accelerate the healing of infected tissues by preventing biofilm formation and to increase the safety of medical devices.

In this context, the following case studies shed light on innovative strategies in infection control and antibiofilm applications. In this study, Patel *et al* [141] investigated how biocomposite scaffolds consisting of 3D printed chitosan, silk fibroin and cellulose nanoparticles (CS/SF/CNPs) can be used for bone regeneration. In their study, they investigated the effects of these materials on macrophage polarization and their osteoimmunomodulatory properties. They produced bioprintable scaffolds by combining chitosan, silk fibroin and cellulose nanoparticles with a 3D printer (figure 5(a)). The developed scaffolds were examined with various characterization methods such as FTIR, XRD and rheological tests and were observed to be mechanically strong, biocompatible and hydrophilic. In *in vitro* experiments, it was observed that CS/SF/CNPs scaffolds promoted the transformation from M1 type (proinflammatory) macrophages to M2 type (anti-inflammatory) macrophages (figure 5(b)). This polarization was evaluated as a supportive effect on tissue healing and bone regeneration. In addition, in experiments with human bone marrow-derived mesenchymal stem cells (hBMSCs), they found that the scaffolds increased osteogenic gene and protein expressions. Significant increases were observed in the expressions of osteogenic genes, especially Runx2, ALP and OPN. *In vivo* experiments using a skull bone defect model in mice showed that CS/SF/CNPs scaffolds significantly increased bone regeneration (figure 5(c)). It was stated that the scaffolds promoted bone healing without the use of growth factors. Huiszoon *et al* [142] developed a system integrated into commercial Foley catheters for the management of catheter-associated urinary tract infections (CAUTI). This system includes flexible electrodes, impedance sensors for bacterial growth detection and biofilm treatment, and a biofilm management prototype that supports the use of low-dose antibiotics. In their study, flexible electrodes and impedance sensors manufactured with 3D printing technology were integrated into the tip of the Foley catheter. These electrodes were designed to create bioelectric effects and control biofilm formation. Continuous impedance measurements were performed for early detection of bacterial growth. The electrodes were optimized to detect the effects of biofilm growth and bacterial metabolism. A low-intensity electric field with a frequency of 20 kHz was applied to the biofilm formed on the inner surface of the catheter. This method aimed to create a synergistic effect in biofilm reduction by enhancing the effect of antibiotics. As a result of the study, a 13% decrease in impedance values was observed in the presence of *Escherichia coli* (*E. coli*). In the control groups, impedance increased by 5.4%.



These results confirmed the real-time monitoring of biofilm formation. BE treatment increased the effectiveness of antibiotics on biofilm and reduced biofilm biomass by up to 75%. The number of planktonic bacteria was found to be significantly lower in BE treatment compared to other methods. The modified catheter preserved basic Foley catheter functions such as urine drainage and balloon inflation. The system is made easy to use with a Bluetooth-controlled mobile application. This integrated system offers an innovative approach for CAUTI management. The system, which combines bacterial detection and biofilm treatment, provides an effective solution for the management of resistant infections by minimizing antibiotic use.

Lee *et al* [143] developed a multilayered airway model fabricated by 3D printing for SARS-CoV-2 infection and antiviral drug testing. The aim of the study was to create a physiologically relevant microstructure and to study SARS-CoV-2 infection dynamics and antiviral efficacy assessments using this model. The research created a model containing human lung cell-derived epithelium, vascular endothelial cells, and collagen-based ECM layers using inkjet bioprinting and microextrusion methods. The model showed susceptibility to SARS-CoV-2 infection due to high expression of ACE2 and TMPRSS2 receptors, and cytopathic effects and barrier disruption were observed in infected cells for 21 days. The results showed that this 3D airway model provides a suitable

platform for studying the effects of antiviral drugs such as remdesivir and molnupiravir, as well as virus infection. This model holds promise for evaluating the efficacy of antiviral candidates by analyzing the dynamics of viral replication, gene expression changes, and host immune responses. Liu *et al* [144] developed two-dimensional (2D) hetero-nanostructures and three-dimensional (3D) printed scaffolds functionalized with immunomodulatory interleukin-4 (IL-4) cytokines to improve bone injury repair. The aim of the study was to create a pro-healing immune microenvironment to optimize bone repair and provide favorable conditions for bone regeneration. In their study, the scaffolds were fabricated with a Bio-X 3D bioprinting device using a polymeric ink. The surfaces were coated with graphene oxide (GO) and black phosphorus (BP) nanosheets to form 2D-3D hetero-nanostructures. GO nanosheets were used to improve cell adhesion, while BP nanosheets stimulated cell growth and osteogenesis by providing sustained phosphate ion release. Immunomodulatory IL-4 cytokines loaded onto the surfaces directed macrophage polarization to M2 phenotype. The effect of scaffolds on bone regeneration was investigated in a rat skull defect model. One volume/tissue volume ratio (BV/TV), bone mineral density (BMD) and new bone area were evaluated by micro-CT. As a result of the study, functional scaffolds with GO and BP hetero-nanostructures significantly increased cell adhesion and proliferation. Live/cell stainings showed that cells adhered more densely to surfaces coated with GO and BP nanosheets. ALP activity and osteopontin (OPN) expression were found to be significantly higher especially in the 3D-Scaf-GOBP functional scaffold group. In the 3D-Scaf-GOBP-Immune group, bone volume/tissue volume (BV/TV) ratio and new bone area were found to be significantly higher compared to the other groups. The scaffolds filled the bone defect and supported significant new bone formation. In the groups treated with functional scaffolds, denser and more integrated bone structure was observed. M2 macrophage phenotype (CD206+ cells) was significantly increased in scaffolds coated with IL-4 loaded GO-BP hetero-nanostructures. This study demonstrated that 3D printed scaffolds functionalized with immunomodulatory cytokines offer a promising solution for bone regeneration. GO and BP hetero-nanostructures improved cell adhesion and proliferation, while IL-4 loading directed macrophage polarization to M2 phenotype, creating an osteogenic microenvironment.

Liang *et al* [145] developed PLGA scaffolds reinforced with nano-hydroxyapatite (nHA) loaded with linezolid for use in the treatment of infected bone defects (IBD) and produced these scaffolds via 3D printing. The aim of the study is to provide a solution that can promote bone regeneration while controlling infection. In their study, PLGA and HA were produced as cylindrical and porous scaffolds via 3D

printing technique. nHA and linezolid were added to the PLGA scaffolds produced via 3D printing, providing antibacterial properties and osteogenic activity. *In vivo* experiments on a rabbit radius defect model revealed that linezolid loaded scaffolds exhibited long-term antibacterial effects against resistant bacteria such as MRSA and accelerated bone regeneration. Linezolid loading was designed to provide antibiotic release. Infected bone defects were created in the forearm bones of New Zealand rabbits. Linezolid-loaded PLGA-HA scaffolds were tested compared to the control groups (empty PLGA and PLGA-HA). New bone formation, bacterial infection control and cellular responses were evaluated by micro-CT, histology, antibacterial tests and biocompatibility analyses. As a result of the study, linezolid-loaded scaffolds were found to effectively inhibit methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The antibacterial effect was found to last for 28 days. Linezolid-loaded PLGA-HA scaffolds were found to provide a higher new bone volume/tissue volume ratio (BV/TV) compared to the control groups. Increased expression of osteogenic proteins (Runx2, OCN, COL-1) was observed. The scaffolds showed high proliferation and differentiation potential on human bone marrow mesenchymal stem cells (BMSCs). No toxic effects were observed in rabbits; liver, kidney and heart tissues were observed to be normal. 3D printed PLGA-HA scaffolds were evaluated as an effective treatment method that offers antibacterial and bone regenerative properties together in infected bone defects. Linezolid-loaded scaffolds were found to accelerate new bone formation while controlling infection. In cellular studies, it was found that the scaffolds supported the proliferation and osteogenic differentiation of bone marrow stem cells (BMSCs). In addition, infection was suppressed and healthy bone formation was provided thanks to linezolid release in infected areas. The results show that these innovative scaffolds are an effective tool in the treatment of infected bone defects and are a strong candidate for clinical applications.

Wu *et al* [146] investigated the use of biopolymer nanoscaffolds containing black phosphorus (BP) for bone implants using 3D printing methods. The aim of the study is to develop effective solutions for bone regeneration and tumor treatment by using the photothermal properties and biocompatibility of BP. The research focused on the combination of natural and synthetic polymers with BP. The polymers included biomaterials such as PLGA, PCL and alginate, and were shown to increase mechanical strength and support the biological effects of BP. It was stated that 3D printed scaffolds support cellular proliferation, angiogenesis and osteogenic activity, and also provide a suitable platform for photothermal therapy. The results revealed that BP-based biopolymer scaffolds have innovative potential in the biomedical field and can be used for personalized approaches in bone

regeneration and tumor treatment. Wang *et al* [147] developed 3D printed PEEK implants modified with hyperbranched poly-L-lysine (HBPL) for infection control and bone regeneration. In the study, PEEK implant surfaces were activated with oxygen plasma and coated with HBPL by two methods: physical adsorption (PEEK-a-HBPL) and chemical bonding (PEEK-g-HBPL). The antibacterial activity of the implants after surface modification was tested on *Staphylococcus aureus* and *E. coli*, and 99.6%–100% antibacterial protection was achieved. Osteoblast cell culture experiments showed that the modified implants increased cell adhesion, proliferation, and osteogenic differentiation. In a rabbit bone infection model, HBPL-coated implants suppressed infection and accelerated new bone formation. The results demonstrated that HBPL-modified PEEK implants are an effective option for the treatment of infected bone defects and bone tissue engineering. Vieira *et al* [148] conducted a study aimed at preventing infection and biofilm formation in medical devices by integrating 1,3-diaryltriazene derivatives into 3D printed hydrogel coatings. The aim of the study was to synthesize new antimicrobial molecules, examine the applicability of these molecules to biomaterials, and evaluate their biocompatibility. Using 3D printing technology, chitosan-sugar based porous hydrogel structures were produced and 1.3-bis(4-nitro-2-(trifluoromethyl)phenyl)triazene (3a) derivative was loaded in an alginate based hydrogel. These coatings were applied to polydimethylsiloxane (PDMS) surfaces and their surface properties were improved. The findings showed that the coatings: Reduced *S. aureus* biofilm formation by 96%; Exhibited antimicrobial and antibiofilm properties; Were safe in terms of biocompatibility. The results suggest that triazene derivatives offer a potential solution in preventing medical device-related infections through 3D-printed coatings, representing an important step towards clinical applications. Li *et al* [149] examined the integration of 3D printing technology into clinical applications in the prevention and treatment of infections. The study specifically addressed innovative strategies to prevent biofilm formation on implant surfaces and provide personalized antibacterial solutions. 3D printing technology has enabled the design of personalized surfaces containing antimicrobial materials, biologically active metal ions, and antibacterial coatings. The study emphasized how these technologies were used in the rapid production of personal protective equipment (PPE) and antiviral medical devices during the COVID-19 pandemic. It was also stated that bacterial adhesion was reduced and infection control was optimized by modifying implant surfaces through 3D printing. The results show that 3D printing technology offers a major innovation in infection prevention and treatment processes and has the potential to revolutionize clinical applications.

Fadilah *et al* [150] investigated the production of functional biomaterials containing antimicrobial components for chronic wound healing through 3D bioprinting. The aim of the study was to develop biomaterial-based solutions that accelerate cellular healing processes while preventing infection. The study designed 3D printed wound dressings and biological scaffolds by combining natural and synthetic polymers (e.g., alginate, chitosan) with antimicrobial agents. These materials were optimized to suppress bacterial infections and enhance tissue regeneration. Antibacterial components prevented biofilm formation and suppressed bacterial growth by over 95%. These biomaterials supported the adhesion and proliferation of cells (fibroblasts). They accelerated wound healing by promoting angiogenesis and regulated inflammation. The results showed that 3D printed personalized wound dressings and scaffolds provide an effective solution for the management of infected chronic wounds and optimize the healing process with antibacterial activity. Guzmán-Soto *et al* [151] addressed the critical role of biofilm formation in the context of tissue and implant infections and comprehensively discussed current *in vitro* and *in vivo* biofilm models used to understand these processes. The study emphasizes the strategic importance of these models for evaluating antibiofilm therapies and ensuring the longevity and effectiveness of biomaterials used in the clinic. Although a direct production method is not presented, the described biofilm models can be considered a critical platform for future testing of the antibacterial performance of surface modifications on implants produced through AM. In this respect, the study provides a methodological contribution not only to biofilm biology but also to experimental validation processes aimed at improving the clinical reliability of AM-based biomaterials.

#### 3.4. Metal-based

Metal-based materials have a wide range of uses in biomedical applications, especially due to their mechanical strength, biocompatibility and controlled degradation properties. In recent years, metallic alloys and surface modification techniques developed for tissue engineering and regenerative medicine applications have been intensively researched in order to meet both clinical needs and improve existing treatment methods. Combining these materials with 3D printing technologies offers innovative solutions in areas such as bone, vascular and nerve regeneration, while also allowing the production of personalized medical devices. Innovative approaches used in metal-based applications generally aim to provide biological and mechanical compatibility together. For example, porous structures increase osseointegration and cellular integration, while surface modifications can support antibacterial properties. Under this heading, the applications of metallic materials in

regenerative medicine, ranging from titanium alloys such as Ti-6Al-4V to magnesium-based biomaterials, are comprehensively discussed. Additionally, the integration of these materials with 3D printing technology demonstrates the potential to create personalized treatment strategies.

Orłowska *et al* [152] investigated the surface modification of highly porous Ti-6Al-4V spinal implants by plasma electrolytic oxidation (PEO) method. The aim of the study was to increase the corrosion resistance of the implants, reduce metal ion release and support osteoblast cell adhesion and proliferation by improving the surface properties. In the study, the surface of implants produced by SLM was modified by PEO technique. This technique created micropores on the surface and enabled the integration of osteogenic ions such as calcium and phosphorus. It was observed that the modification: significantly increased corrosion resistance; reduced metal ion release by 50%; provided a homogeneous surface for cell adhesion and proliferation. The results showed that PEO-modified surfaces provide a biocompatible and functional solution in spinal implants used for the treatment of degenerative diseases of the spine. However, it was emphasized that further biological studies are necessary to evaluate the effectiveness of osteointegration. Martinez *et al* [153] investigated the potential of biodegradable Mg-0.45Zn-0.45Ca (ZX00) alloy for provisional orthopedic implants. The study comprehensively evaluated the corrosion behavior, biocompatibility, and bone-implant interaction of ZX00 screws in both *in vitro* and *in vivo* environments. The aim was to determine whether ZX00 alloy is a biocompatible alternative that promotes bone healing. ZX00 screws were extruded using high purity Mg (99.9999%), Zn (99.9999%), and Ca (99.95%) and CNC machined. Three main regions were analyzed: screw head, screw valley, and tip. EBSD analysis showed larger grains in the screw head and a finer structure in the groove. The initial surfaces were smooth ( $R_a = 0.3\text{--}0.4\ \mu\text{m}$ ) and covered with a thin oxide layer. ZX00 screws were tested in  $\alpha$ -MEM medium for 3, 6, 14, 21 and 28 days. The corrosion rate was determined as  $0.74\ \text{mm year}^{-1}$  in the first 3 days. It was seen that this rate stabilized as  $1.04\ \text{mm year}^{-1}$  at the end of 28 days. The thickness of the corrosion layer was found to increase from  $6.2\ \mu\text{m}$  to  $56.8\ \mu\text{m}$  from 3 to 28 days. ZX00 screws were tested in sheep tibias for 6, 12 and 24 weeks. They observed that thin ( $19\text{--}61\ \mu\text{m}$ ) corrosion layers were formed in the cortical bone and thicker ( $65\text{--}174\ \mu\text{m}$ ) corrosion layers were formed in the intramedullary space. Histological analysis showed that new bone formation and osteoid deposition occurred. At 24 weeks, high bone-implant contact (BIC) was observed around the screws. The new bone directly combined with the corrosion products, confirming that the implant was biocompatible.

Chen *et al* [154] investigated the potential of magnesium-based biomaterials (MBM) in tissue engineering and regenerative medicine applications. The study investigated the effectiveness of MBMs in bone, vascular and nerve regeneration by optimizing their properties such as mechanical strength, biocompatibility and biodegradability. The study showed that magnesium ions released by the degradation of MBMs accelerate bone tissue formation, increase osteoblast cell proliferation and activate PI3K/Akt and OPG/RANKL/RANK signaling pathways, supporting osteogenic differentiation. In addition, it was stated that magnesium ions promote the expression of angiogenic factors such as VEGF and bFGF in vascular tissue and contribute to vascular formation by supporting endothelial cell growth. In studies conducted for nerve tissue regeneration, it was observed that MBMs increase Schwann cell proliferation and facilitate nerve repair with their anti-inflammatory effects. It has been stated that these materials, which reduce the risk of infection thanks to their antibacterial properties, accelerate wound healing and tissue regeneration by regulating inflammation. The results show that MBMs offer an innovative and effective solution for bone, vascular and nerve regeneration in tissue engineering and regenerative medicine applications. Bandyopadhyay *et al* [155] investigated the potential of Ti-Ta-Cu alloys for new generation load-bearing implants. In the study, tantalum (Ta) and copper (Cu) were added to  $\text{Ti}_3\text{Al}_2\text{V}$  alloy using AM method to optimize biomechanical strength, biocompatibility and antibacterial properties. The study showed that addition of 3 wt% Cu increased the antibacterial activity against bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* on the implant surface by 78%–86%. In addition, 10 wt% Ta addition was found to improve biocompatibility and accelerate early osseointegration. *In vivo* tests on rat models revealed that  $\text{Ti}_3\text{Al}_2\text{V}\text{--}10\text{Ta}\text{--}3\text{Cu}$  alloy supports osteoid formation at the bone-implant interface and does not cause inflammatory response. In mechanical tests,  $\text{Ti}_3\text{Al}_2\text{V}\text{--}10\text{Ta}\text{--}3\text{Cu}$  alloy exhibited high fatigue resistance, superior shear strength and improved tribological properties. In addition, 3% Cu addition increased strength by forming intermetallic  $\text{Ti}_2\text{Cu}$  phase, while 10% Ta addition increased the elastic modulus, making the structure more suitable for bone-like mechanical properties. The results show that  $\text{Ti}_3\text{Al}_2\text{V}\text{--}10\text{Ta}\text{--}3\text{Cu}$  alloy offers an innovative and versatile solution for new generation load-bearing metallic implants thanks to its biocompatibility and antibacterial properties.

Zhou *et al* [156] conducted a comprehensive review on the production of Ti-based multi-metal alloys by 3D printing and discussed the potential of these materials in bone regeneration applications. The study detailed the effects of these alloys on bone repair and integration by optimizing their mechanical, angiogenic, immune-regulatory and osteogenic

properties. The direct effects of the physicochemical properties of Ti-based materials produced by 3D printing, such as roughness, hydrophilicity and corrosion resistance, as well as mechanical properties such as pore shape, size and porosity ratio on osteogenesis were emphasized. In particular, porous structures induced contact osteogenesis by providing rapid neo-vascularization around the implant and accelerated bone integration. Li *et al* [157] developed 3D-printed titanium implants with micro/nano hierarchical surfaces for infection control and osteogenic induction in infected bone defects. The study designed a dual carrier system that enables the independent release of Ag<sup>+</sup> and Sr<sup>2+</sup> ions, thus aiming to promote both antibacterial activity and bone formation. Implant surfaces were prepared using alkaline-heat (AH) treatment and polydopamine (PDA) coating, followed by loading of Ag nanoparticles and Sr ions onto the surface. In mechanical tests, the elastic modulus of AH-Sr-AgNPs implants was found to be very similar to cancellous bone. Over 98% antibacterial efficacy was observed against *E. coli* and *S. aureus* bacteria, and an anti-inflammatory healing environment was achieved through increased M2 macrophage polarization. Sr<sup>2+</sup> ions were shown to support osteoblast activity (ALP, Runx2, and COL-1 expression) during osteogenic differentiation. In a rabbit femur defect model, the bone-to-implant contact rate was determined to exceed 75%. These findings demonstrate that surface modifications in AM-fabricated titanium implants have the potential to prevent infection and enhance osseointegration. Yue Zhang *et al* [158] investigated the mechanical properties, biocompatibility, and degradation behavior of a biodegradable Mg-based surgical stapler for colonic anastomosis both *in vitro* and *in vivo*. In the study, a double-layer coating consisting of micro-arc oxidation (MAO) and polylactic acid (PLLA) layers was applied to 0.3 mm diameter AZ31 Mg alloy wires to control the degradation rate. The resulting wires were formed into 'U' and 'B'-shaped staples and tested on porcine colons and beagle dogs. The coating provided high mechanical stability for the first 7 days, and the staples were completely biodegraded after 90 days. Histological examinations revealed that tissue healing occurred smoothly and Mg ions did not accumulate in the organs. This study is important for the design of biodegradable metal implants produced using AM methods, because it has been shown that Mg alloy supports tissue healing and provides long-term biodegradability when used with appropriate coating techniques. Bricha *et al* [159] presented a comprehensive review evaluating the design parameters, biological and mechanical properties, and surface modifications of porous metallic implants produced using AM (SLM, EBM) methods. The study reported that pore sizes (400–900 µm) support osteoblast proliferation and vascular formation, while porosity levels of 40%–70% enhance cell nutrition and oxygen exchange,

strengthening bone-implant interactions. Furthermore, it was emphasized that complex porous structures can be produced using SLM and EBM techniques, and that EBM, in particular, reduces stress concentrations thanks to its high-temperature stability. These findings demonstrate that AM-based porous metallic implants, which combine biocompatibility and mechanical strength, offer innovative and long-term successful solutions for bone tissue regeneration.

Hauschild *et al* [160] evaluated the effects of different topographic features of titanium-based implant surfaces and titanium nitride (TiN) coating on adhesion, viability and proliferation of human dermal fibroblasts (HDFa). The study aimed to develop highly biocompatible and mechanically stable surfaces in order to provide renewal of the skin-prosthesis interface in transcuteaneous osseointegrated prosthesis systems (TOPS). It was stated that porous structures (61 ± 8% porosity) supported fibroblast adhesion and filopodia formation. Flat and TiN coated surfaces increased cellular proliferation but strengthened the migration tendency of fibroblasts. It was observed that TiN coating increased wettability but limited proliferation by reducing cellular density and linear array formation tendency. After 24 h, cellular viability on porous surfaces showed a more homogeneous distribution compared to flat surfaces. In the 7-day study, cellular density and confluence increased on smooth surfaces, while proliferation occurred more slowly on porous surfaces. The study provided valuable information for the development of a biocompatible and stable interface for transcuteaneous implants. However, it was stated that further studies are required on the effects of TiN coating. Cao *et al* [161] evaluated the mechanical properties, biodegradation behaviors, and biosafety of porous Zn-1Mg-0.1Sr alloy scaffolds produced by 3D printing technology. The study provides important findings for the development of biodegradable metallic materials that can be used in the treatment of bone defects. Zn-1Mg-0.1Sr alloy produced using SLM method exhibited a microporous structure and showed advantageous properties in biomedical applications. Zn-1Mg-0.1Sr alloy exhibited compressive strength of 33.71 ± 2.51 MPa, yield strength (YS) of 27.88 ± 1.58 MPa, and elastic modulus of 2.3 ± 0.8 GPa. Compared with pure Zn skeletons (CS: 16.17 ± 0.71 MPa, YS: 10.21 ± 0.38 MPa, E: 0.8 ± 0.1 GPa), Zn-1Mg-0.1Sr alloy showed significantly higher strength. The flexibility of the porous structure reduced the stress shielding effect, providing mechanical properties similar to human bone. As a result of 14-day immersion tests, the alloy skeleton showed 12.82 ± 0.55% weight loss and reached a corrosion rate of 0.36 ± 0.01 mm year<sup>-1</sup>. The release of Zn and Sr ions (Zn<sup>2+</sup>: 2.14 ± 0.82 mg/l, Sr<sup>2+</sup>: 0.34 ± 0.14 mg/l) showed a stable increase. The pH level increased to 7.68 ± 0.01 at the end of the fifth day and

stabilized in the range of  $7.61 \pm 0.09$  for 14 days. The pore sizes were designed as  $550 \pm 27 \mu\text{m}$  and exhibited a homogeneous structure with  $70 \pm 2\%$  porosity. XRD analyses revealed that the Zn-1Mg-0.1Sr alloy contained dendritic  $\alpha$ -Zn phase and eutectic components such as  $\text{MgZn}_2$ ,  $\text{Mg}_2\text{Zn}_{11}$ ,  $\text{SrZn}_{13}$ . When MC3T3-E1 osteoblast precursor cells were cultured with 10% and 20% extracts, the cytotoxicity level was classified as 0 (harmless and non-toxic). 100% extracts were classified as cytotoxicity level 4 (severely toxic). It has been stated that the release of Zn and Mg ions promotes cell proliferation and bone tissue regeneration.

Xiao *et al* [162] comprehensively investigated the biological and mechanical properties of 3D printed PCL/ $\text{Fe}_3\text{O}_4$ @ZIF-8 magnetic nanocomposite materials for the treatment of infected bone defects. The study shows that these nanocomposites offer an innovative solution for bone regeneration and infection control by offering antibacterial activity and osteogenic potential. As a result of the study, PCL/ $\text{Fe}_3\text{O}_4$ @ZIF-8 scaffolds exhibited a square porous structure in the range of 400–800  $\mu\text{m}$ , and the surface roughness increased with increasing  $\text{Fe}_3\text{O}_4$ @ZIF-8 ratio. The compressive strength ( $21.50 \pm 0.26$  MPa) and elastic modulus ( $31.22 \pm 0.98$  MPa) values were significantly improved as the  $\text{Fe}_3\text{O}_4$ @ZIF-8 concentration increased. Thermogravimetric analysis (TGA) showed that PCL/ $\text{Fe}_3\text{O}_4$ @ZIF-8 materials were stable in the range of 30°C–250°C. Controlled  $\text{Zn}^{2+}$  release showed a rapid increase during the first 12 h, then continued continuously for 7 days. PCL/15% $\text{Fe}_3\text{O}_4$ @ZIF-8 scaffolds showed 83.49% and 92.69% antibacterial adhesion efficiency against *S. aureus* and *E. coli*, respectively. SEM images confirmed the precipitation and disruption of bacterial cell membranes. Subcutaneous infection model and cranial defect model showed that  $\text{Fe}_3\text{O}_4$ @ZIF-8 containing scaffolds reduced inflammatory response and bacterial colonization. PCL/10% $\text{Fe}_3\text{O}_4$ @ZIF-8 promoted the adhesion and proliferation of rat bone marrow mesenchymal stem cells (BMSCs). A significant increase in the expression of osteogenic genes such as ALP, COL-1, RUNX2 and OCN was observed. It has been reported that osteoblast differentiation is promoted by activating the Wnt/ $\beta$ -catenin signaling pathway. In 6 and 12 weeks *in vivo* analysis, PCL/10% $\text{Fe}_3\text{O}_4$ @ZIF-8 scaffolds were shown to accelerate new bone formation and regeneration in the infected environment.

Yazdani *et al* [163] conducted a comprehensive study on the development and characterization of Ti-10Nb-10Zr-5Si-5Sn-5Cu (TNZSSC) alloy. The study investigated the mechanical, thermal and corrosion properties of the newly developed amorphous metallic glass alloy and evaluated its suitability for biomedical applications. The alloy was produced using arc melting and gas atomization methods and optimized in powder form for 3D printing technology. TNZSSC alloy showed a better mechanical compatibility with

bone tissue by reducing the elastic modulus value to 60 GPa compared to TNZ alloy. The hardness of the alloy was measured as 12 GPa, which exhibited superior mechanical performance than TNZ alloy (33% higher). TNZSSC alloy offered high wear resistance with an H/E ratio (hardness/elastic modulus) of 0.2, compared to 0.06 in TNZ alloy. TNZSSC alloy exhibited lower corrosion current density ( $0.32 \mu\text{A cm}^{-2}$ ) and corrosion rate ( $0.0034 \text{ mm year}^{-1}$ ) compared to TNZ alloy. A passive oxide layer ( $\text{TiO}_2$ ,  $\text{Nb}_2\text{O}_5$  and  $\text{SiO}_2$ ) was formed on the surface of the alloy and this layer increased the corrosion resistance. It was stated that TNZSSC alloy has a completely amorphous structure. The  $\beta$  phase dominant structure of the alloy optimized the mechanical and corrosion performance. TNZSSC alloy, to which Si, Sn and Cu elements were added, provided reduction in grain size and phase homogeneity compared to TNZ alloy. TNZSSC alloy was converted to powder form by gas atomization to provide high sphericity ( $>90\%$ ) and fine particle sizes ( $<45 \mu\text{m}$ ). It was emphasized that these powders are ideal for biomedical 3D printing applications with low oxygen, nitrogen and hydrogen content. Davoodi *et al* [164] provide an overview of additively manufactured metallic biomaterials, discussing their mechanical properties and applications in biomedical fields. The study highlights the need to optimize processing parameters to enhance the performance of metallic scaffolds in tissue engineering. Li *et al* [118] investigated the production of biodegradable porous Mg using AM techniques. Their findings suggest that these scaffolds have mechanical properties that closely mimic those of natural bone, making them suitable for bone tissue engineering applications. The study highlights the importance of controlling the microstructure to increase biocompatibility and support cell growth.

### 3.5. Soft tissue regeneration

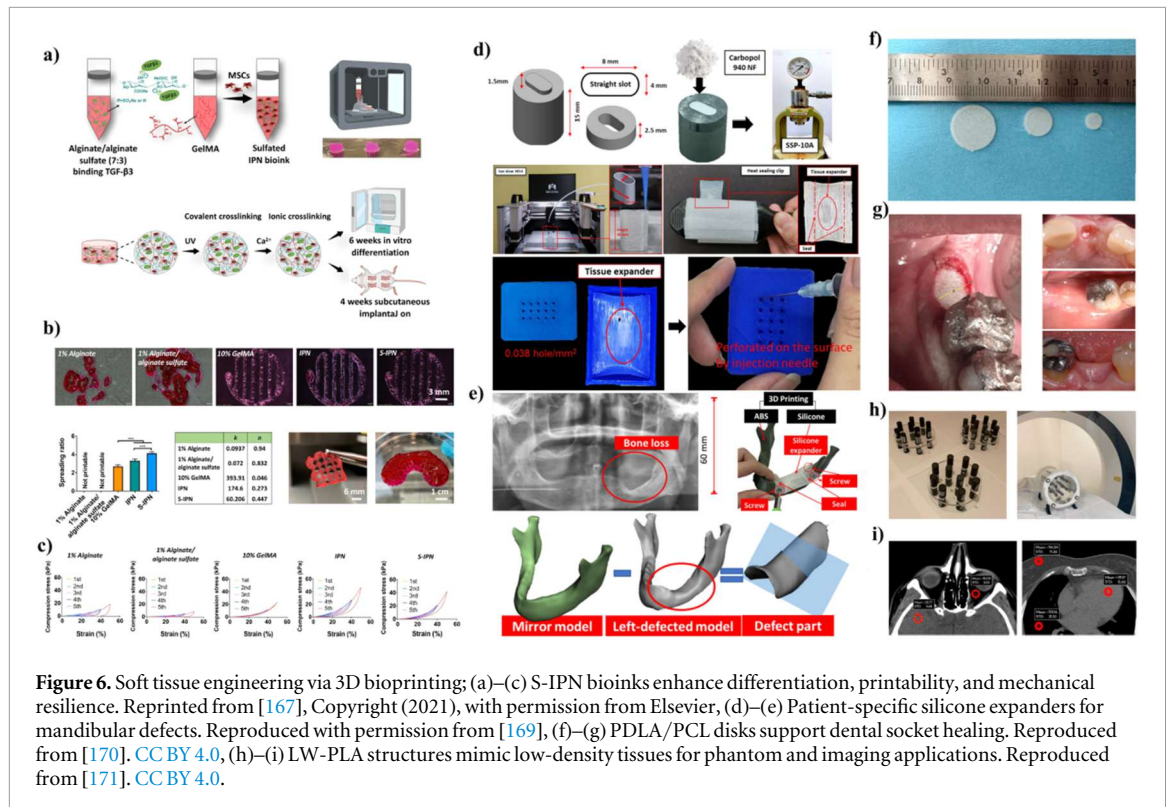
Soft tissue regeneration is an important area for the functional recovery of flexible tissues of the human body. The biomechanical strength, flexibility and biological activities of structures such as muscle, skin, vascular and nerve tissues are an important focus in tissue engineering. In particular, complete recovery of soft tissues damaged by trauma, surgical operations or chronic diseases can be made more effective with bioengineering-based solutions. In cases where traditional treatment methods are inadequate, innovative technologies and biomaterials developed in the field of regenerative medicine stand out as important tools that support this process. 3D printing technology has created a significant paradigm shift in the field of soft tissue engineering. This technology enables personalized treatment approaches by providing controllability of biomaterials at the micron level. Innovative platforms, especially biocompatible hydrogels, nanocomposites, hybrid scaffolds and patient-specific

designs, have the potential to improve the biological and mechanical properties of soft tissues. In addition, additional functions of structures produced from biodegradable materials, such as controlled drug release and cellular integration, play a critical role in accelerating healing processes. Under this heading, innovative approaches using 3D printing technologies for soft tissue regeneration are discussed. Examples of mechanically strong yet flexible structures such as femtosecond laser-produced chainmail architectures, hydrogels with improved mechanical properties, phantoms that mimic radiological tissues, polymer-based scaffold systems, and patient-specific designs represent advanced solutions in this field. These studies, which aim to overcome the biological and mechanical challenges faced by soft tissue engineering, have the potential to transform the clinical applications of regenerative medicine.

Jonušauskas *et al* [165] focused on the production and testing of 3D microchainmail structures that support cell growth and can be used for regenerative medicine. The aim of the study was to produce flexible structures with high mechanical strength and biocompatibility. For this purpose, femtosecond laser direct writing (DLW) method was used. In particular, the study examined how the structures can be made suitable for soft tissue regeneration using the hard polymer SZ2080. The biocompatibility effects of different photoinitiators (IRG and BIS) were tested on structures produced with SZ2080 material. It was observed that all structures showed high performance in terms of cell adhesion and proliferation, even providing 30% better cell proliferation compared to flat surfaces. It was shown that chainmail structures can be printed in just minutes with optimizations that increase production speed and can be quickly integrated into medical procedures. In this study, it was demonstrated that the chain armor structures produced are an effective platform for cell growth and tissue regeneration. It was observed that cells can grow freely on the structures and the structure is reusable. It was also emphasized that the chain armor can offer a general solution instead of special designs for individual patients. Guo *et al* [166] conducted a comprehensive study to improve the mechanical properties of Gelatin Methacryloyl (GelMA)-based hydrogels that can be produced with 3D printing. GelMA is a widely used material in tissue engineering applications due to its biocompatibility, biodegradability and photopolymerization properties. However, the limited mechanical strength and rapid degradation of these hydrogels make them inadequate for broader biomedical applications. The aim of the study is to increase the mechanical strength of GelMA and provide a more functional use in soft tissue engineering and 3D bioprinting technologies. In this context, physical and chemical enhancement strategies were investigated at both micro and nanoscales in the study, and the 3D printing compatibility and biological activity

of modified GelMA-based hydrogels were evaluated in detail. In the study, various reinforcement strategies were applied from the monomer level to the nanoscale, and the effects of these modifications on cell adhesion, proliferation and tissue regeneration were analyzed. For example, new cross-linked networks were created using interpenetrating networks (IPNs), mechanical strength was increased with nanomaterial additives, and ionic cross-linking methods were applied to improve layer-to-layer adhesion. The study not only expands the potential of GelMA as a bioprinting ink, but also offers unique application opportunities for different biomedical fields such as vascular, myocardial, nerve, skin, and cartilage tissue engineering.

The regeneration of cartilage tissue via bioprinting using sulfated interpenetrating network (IPN) bioinks was investigated by Bin Wang *et al* [167] (figure 6(a)). The aim of the study was to develop an optimized bioink to both increase mechanical strength and create phenotypically stable cartilage tissue by controlled release of growth factors. The combination of Gelatin Methacryloyl (GelMA) and alginate sulfate was used to form the IPN structure. It provided high binding affinity to growth factors such as TGF- $\beta$ 3 and provided controlled release (figure 6(b)). The double cross-linked structure increased mechanical strength and provided elasticity. IPN and S-IPN (sulfated IPN) structures exhibited better printing compatibility and high accuracy than conventional bioinks. It was found that S-IPN structures showed minimal deformation even after 50% compression (figure 6(c)). The bioinks supported stable cartilage tissue production for 42 days due to encapsulated TGF- $\beta$ 3. Osteogenic differentiation was suppressed and cartilage cell phenotype was preserved. Sulfated IPN bioinks are a promising strategy for cartilage tissue regeneration due to the sustained release of TGF- $\beta$ 3 and high mechanical strength. The usability of these bioinks in a single-step implantation strategy offers potential for bioprinting applications in clinical settings. Russo Serafini *et al* [168] investigated the use of medical grade polycaprolactone (mPCL) based scaffolds produced by melt electrowriting (MEW) in the treatment of abdominal hernias and vaginal prolapse. The study investigated the hypothesis that mPCL scaffolds with biodegradable properties could enhance soft tissue regeneration and mechanical integration performance by enriching them with platelet-rich plasma (PRP). The ovine model used provided a comprehensive platform to evaluate the effects of scaffolds on abdominal and vaginal tissues. The main purpose of the study was to solve the biocompatibility problems of existing polypropylene (PP) meshes and to develop a more flexible, biointegrable scaffold alternative. As a result of the study, they observed that mPCL scaffolds mimic the mechanical properties of natural soft tissue by presenting an anisotropic structure consisting of



**Figure 6.** Soft tissue engineering via 3D bioprinting; (a)–(c) S-IPN bioinks enhance differentiation, printability, and mechanical resilience. Reprinted from [167], Copyright (2021), with permission from Elsevier, (d)–(e) Patient-specific silicone expanders for mandibular defects. Reproduced with permission from [169], (f)–(g) PDLA/PCL disks support dental socket healing. Reproduced from [170]. [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/), (h)–(i) LW-PLA structures mimic low-density tissues for phantom and imaging applications. Reproduced from [171]. [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

curved and straight fibers. The scaffolds have smaller pore sizes ( $500 \mu\text{m} \times 1000 \mu\text{m}$ ) and thinner fiber diameters ( $43.6 \pm 7.7 \mu\text{m}$ ) than PP meshes, resulting in higher surface area/volume ratio and better tissue integration. Mechanical tests showed that mPCL scaffolds provided good support with the tissue but were less stiff than PP meshes. PRP-enriched mPCL scaffolds supported early tissue integration with better vascularization and collagen infiltration. Compared to the PP mesh group, mPCL scaffolds showed less inflammatory response and a more balanced macrophage polarization (trending toward M2). Neovascularization was concentrated around the PP mesh group and was regularly distributed among the fibers of mPCL scaffolds. The PP mesh group resulted in extensive fibrosis and collagen deposition, while the mPCL scaffolds showed more regular and homogeneous tissue regeneration. After six months, more mature collagen type I formation was observed around the mPCL scaffolds.

Pisani *et al* [172] evaluated various fabrication techniques such as solvent casting (SC), electrospinning (ES), and 3D printing (3DP) to develop bioartificial scaffolds (BSs) for soft organ transplantation alternatives. This study analyzed the morphological, biological, and mechanical properties of scaffolds produced from PLA-PCL (polylactide-co-caprolactone) copolymer and examined the effect of different fabrication methods on the final structure. In addition, the advantages of hybrid scaffolds (HS) created by combining electrospinning and 3D printing were highlighted. The aim of the study was to optimize the design of advanced bioartificial scaffolds that

mimic soft tissue properties suitable for transplantation and are biocompatible. SC produced scaffolds with the lowest porosity and poor mechanical properties. ES provided high porosity, cell adhesion, and biocompatibility with its nanofiber networks. 3DP enabled the fabrication of structures with high mechanical strength but limited porosity. Hybrid scaffolds formed by combining ES and 3DP showed superior performance in terms of both high mechanical strength and cellular compatibility. The combination of nanofibers obtained with ES with harder bases produced with 3DP increased cell adhesion and growth. 83% and 127% cell viability was observed in SC and ES scaffolds. In 3DP scaffolds, it was more difficult to hold cells on the surface due to porosity. Cell adhesion and viability in HSs increased significantly and the entire surface was homogeneously cellularized. SC, ES and 3DP scaffolds showed different hardness values. In particular, hybrid scaffolds (20% and 50% infill) provided suitable mechanical properties for soft tissue regeneration. 3DP scaffolds produced with 100% infill were not found suitable for soft tissue applications because they were too hard. Hybrid scaffolds offer promise in developing alternatives for organ transplantation by offering biocompatible structures. The study not only highlighted the impact of manufacturing methods on the final structure, but also demonstrated how the hybrid approach could play an important role in tissue engineering by enhancing cell adhesion and improving mechanical compliance. Kerstin Rabel *et al* [173] investigated the effects of 3D printed biomaterials used in implant-supported prostheses on soft tissue integration (STI).

The study examined how surface properties and cellular response differ when temporary and permanent biomaterials containing methacrylate-based photopolymers and hybrid ceramic-methacrylate components are produced by 3D printing and conventional methods (subtractive manufacturing). Analyses of cellular functions of gingival fibroblasts (GF) evaluated the effects of the production method and composition of the biomaterials on cell adhesion, morphology, metabolic activity and proliferation. The study aimed to reveal how effective 3D printed biomaterials are in supporting STI compared to conventional methods. As a result of the study, 3D printed materials showed lower GF metabolic activity and proliferation compared to materials produced by conventional methods. Materials produced by subtractive method (perm\_m, temp\_m) and 3Y-TZP control group exhibited higher cell density and morphological fidelity. In 3D printed temporary (temp\_p) and permanent (perm\_p) materials, mitochondrial metabolic activity and DNA concentration were significantly lower. This was attributed to the surface chemistry of 3D printed materials and potential elution products. Eluates of 3D printed materials were found to contain certain chemical components that increased fibroblast cytotoxicity. Minor differences were observed in surface properties between temporary and permanent biomaterials. However, the differences between 3D printing and subtractive methods were more pronounced. Permanent biomaterials (perm\_p, perm\_m) provided better cell adaptation and proliferation than temporary ones.

Huang *et al* [169] developed patient-specific gingival soft tissue expanders for the treatment of large mandibular bone defects. In this study, a soft tissue expander consisting of swellable polymer tablets placed in a silicone membrane using 3D printing technology was designed and tested (figure 6(d)). This device aims to overcome the limitations of traditional hydrogel-based expanders and provide patient-specific structures that will precisely adapt to the shape of the bone defect. The aim of the study is to precisely control the expansion volume and provide a biocompatible solution that optimizes surgical processes. Silicone expander models based on the complex geometries of mandibular bone defects were developed using computer-aided design (CAD) software. Data obtained from CT images of the defect areas were processed to provide symmetrical reconstruction of asymmetric defects. Swellable polymer tablets were used to provide high volume expansion and biocompatibility. Liquid silicone membranes were 3D printed to produce complex structures and provide a biocompatible environment. This study demonstrated the potential of patient-specific silicone expanders to improve soft tissue integration in large mandibular bone defects (figure 6(e)). The expander design shows promise in terms of volume accuracy, biocompatibility, and tissue safety. Beyond clinical applications, it could set a new standard for the use of 3D printing technology in

personalized medical devices. De Angelis *et al* [170] conducted a clinical study examining the effectiveness of 3D printed biopolymers to support soft tissue healing after tooth extraction. This study investigated the effectiveness of biopolymer discs (figure 6(f)) containing poly-D-lactic acid (PDLA) and hydroxyapatite (10%) and poly- $\epsilon$ -caprolactone (PCL) and beta-tricalcium phosphate (20%) in closing extraction sockets. The aim was to provide an economical solution that is fully biocompatible, biodegradable and does not require a second surgical intervention. In this context, different approaches were tested by creating three groups: PDLA discs (Test 1), PCL discs (Test 2) and a control group without any graft material (figure 6(g)). PDLA-Hydroxyapatite is known to increase osteogenic activity and accelerate soft tissue healing. PCL- $\beta$ -Tricalcium Phosphate provided long-term stability by showing high elasticity and biocompatibility properties. In both test groups, the discs were placed inside the gingival tissue and fixed with the cross-matrix suture method. In the control group, the extraction socket was left open and collagen sponge was used only for bleeding control. Patients were regularly followed up for a 6-week postoperative recovery period. As a result of the study, it was observed that PDLA and PCL discs provided faster and more regular tissue closure in posterior tooth extractions compared to the control group. In the test groups, the average open area decreased from 46.5 mm<sup>2</sup> to 0.6 mm<sup>2</sup>, while in the control group it decreased from 45.6 mm<sup>2</sup> to 1.2 mm<sup>2</sup>. These results were found to be statistically significant ( $p < 0.05$ ). No complications such as inflammation, infection or pain were observed in any group. This supports the biocompatibility of the biopolymers used. These biopolymer discs offer promise for socket preservation after tooth extraction by offering an economical solution. They also allow for individualized treatments thanks to bioprinting technology. This study has shown that biopolymers produced with 3D printing provide an effective solution for closing extraction sockets. PDLA and PCL-based materials accelerated soft tissue healing and minimized complications. Bergemann *et al* [174] developed patient-specific 3D printed cutting guides to optimize the extended trochanteric osteotomy (ETO) procedure used in revision total hip arthroplasty (rTHA) procedures. ETO is a surgical technique used to visualize the intramedullary canal and remove the femoral stem. However, complications such as fractures, soft tissue damage, and incorrect osteotomy that may occur during the procedure can make this procedure technically challenging. The aim of the study was to increase surgical precision and reduce complication rates by developing cutting guides that are compatible with patient anatomy using 3D printing technology. This study demonstrated that patient-specific cutting guides produced by 3D printing are effective in increasing surgical precision in ETO procedures. Tests on both synthetic and cadaveric femurs demonstrated that these guides can reduce complications by increasing osteotomy accuracy.

Baniasadi *et al* [175] developed 3D printed scaffolds for soft tissue regeneration using xanthan gum (XG)/CNC. The authors reported excellent swelling ratio, porosity and mechanical properties of the scaffolds that can be applied for soft tissue regeneration. In addition, they observed that these scaffolds provided better adhesion, differentiation and proliferation of liver cancer cells. Özsoykal and Yurt [171] have developed a new density-adjustable 3D printing technique to produce phantoms that can mimic soft tissue radiological features. In the study, Light PLA (LW-PLA) filament, which has the ability to foam under the effect of temperature, was used, unlike standard PLA filaments (figure 6(h)). This innovative filament made it possible to create prints in a wide range of HU (Hounsfield Unit) to mimic low-density tissues (e.g. lungs) and other soft tissues. The main purpose of the study was to develop a technique that can produce low-density and homogeneous tissues with this new filament and to evaluate the radiological compatibility of this method. The research was carried out in three main stages. First, the radiological features of LW-PLA samples printed at different temperatures and flow rates were examined with CT scans (figure 6(i)) for the analysis of radiological features. Then, the consistency of the results was analyzed in repeated processes with the same printing parameters for reproducibility testing. Finally, to investigate the effects of size and printing speed, the effects of printing speed and size on physical density and radiological properties were evaluated in samples of different sizes. As a result of the study, low-density tissues produced with LW-PLA successfully mimicked many soft tissues including lungs. It was determined that additional modifications were required for higher-density structures such as compact bones. Low printing speeds and large-diameter samples provided significant improvements in homogeneity (STD<sub>xy</sub> and STD<sub>z</sub>). Strong linear correlations were found between flow rate and density ( $R^2 > 0.99$ ). Schwab *et al* [176] investigated critical aspects of printability and shape fidelity of bioinks used in 3D bioprinting. They emphasize the importance of achieving high shape fidelity to ensure that printed structures accurately reflect intended designs. The study discusses various factors that affect printability, including the rheological properties of bioinks, which are necessary to maintain cell viability during the printing process.

#### 4. Future perspective

AM's advances in biomaterial integration will not only transform current healthcare systems, but will also fundamentally change the future of medicine by redefining the boundaries between human biology and engineering. In order to fully realize the potential of the AM technology discussed in this study in biomaterial applications, certain shortcomings and current limitations need to be addressed. Future

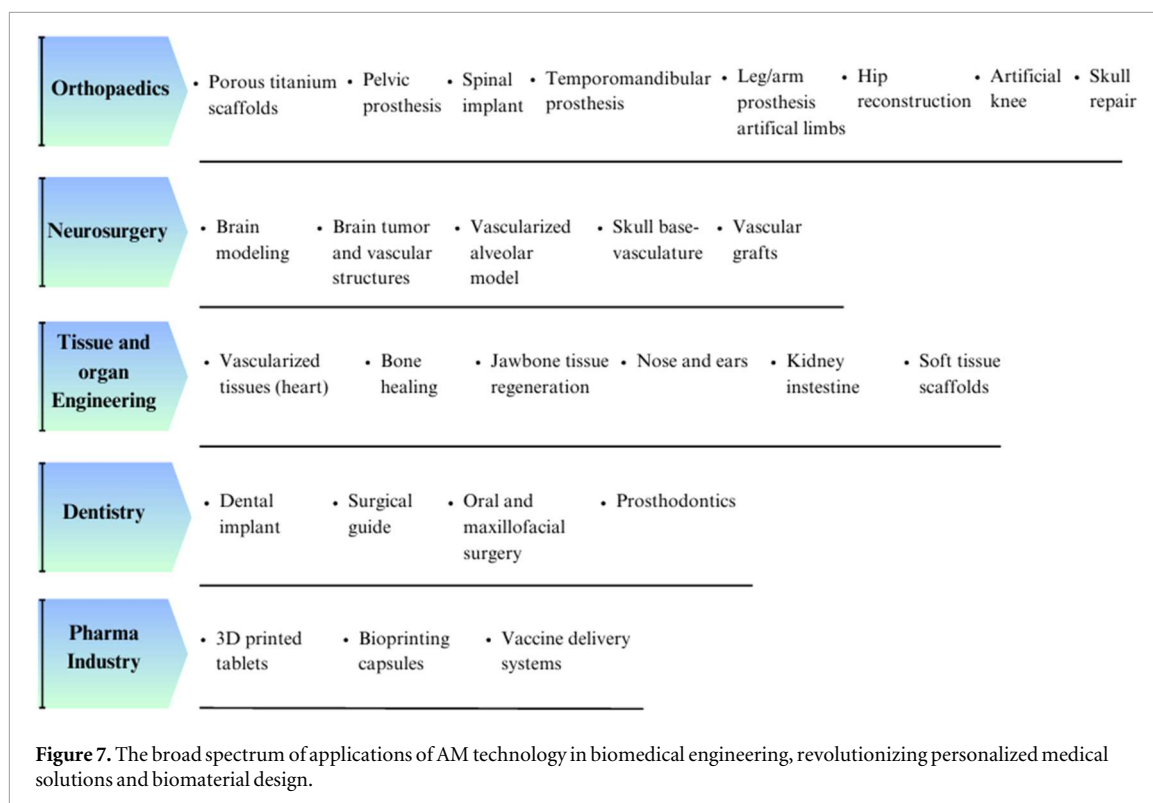
research should focus on improvements at both technical and application levels.

- **Improving material properties:** Material development studies are critical for polymer, ceramic and metal-based biomaterials to perform better in AM processes. New bioengineering strategies need to be developed to reduce surface roughness, increase mechanical strength and optimize biocompatibility. In particular, microstructural control of AM techniques used in materials such as hydroxyapatite and titanium alloys should be increased.
- **Integration of advanced processing techniques:** Advanced post-processing methods need to be developed to solve problems such as dimensional accuracy and surface quality of structures produced with AM. Methods such as laser surface processing and hot isostatic pressing should be integrated to increase mechanical performance.
- **Development of functional structures:** Especially in bioprinting technologies, it is important to better understand cell-material interactions and create multi-material structures that support cellular functions. Research on the development of bioink formulations to produce functional tissue engineering scaffolds should accelerate.
- **Clinical application and regulation:** Regulatory approval processes for clinical applications of AM-produced biomaterials remain a limiting factor. Long-term *in vivo* studies and test protocols documenting the biocompatibility of personalized implants and other biomedical structures are needed for clinical use. In addition, ethical concerns and lack of standards must be addressed.
- **Data-driven design and modeling:** Artificial intelligence and data analytics have great potential for design optimization and material performance prediction in AM processes. In the future, data-driven simulations and modeling tools may enable the creation of more complex and effective biomaterial structures.

As a result, in order for AM technology to reach its full potential in biomaterial applications, extensive research needs to be conducted in areas such as material development, optimization of manufacturing processes, and clinical application integration (figure 7). These trends will further strengthen the role of AM in biomedical engineering and contribute to the widespread use of personalized medical solutions.

#### 5. Conclusion

Advances in AM technologies are playing a transformative role in the development of biomedical engineering. These methods enable personalized and



biocompatible solutions for a wide range of applications, from implants to tissue engineering scaffolds and medical devices. Bioprinting and laser-based manufacturing techniques, along with innovations in materials science, are facilitating the production of structures that can perform biological functions and mimic human tissue. The findings in this review summarize the contributions of AM to biomedical applications under the following headings:

- **Personalization and Precision:** AM methods, combined with bioprinting and advanced manufacturing techniques, enable the high-precision production of personalized prosthetics, biomedical devices, and tissue engineering scaffolds.
- **Metal and Ceramic Biomaterials:** Processing materials such as titanium, magnesium, and hydroxyapatite in AM processes improves the mechanical and biological performance of implants. However, the presentation of hydroxyapatite as the ‘preferred’ material alone does not reflect the diversity in the literature; Biodegradable metals, nanostructured compounds, and biomimetic designs are also among the future research areas.
- **Antibacterial Strategies:** Surface modifications and antibacterial coatings on AM-based implants are critical for preventing infections and increasing clinical success rates.
- **Bone Regeneration and Soft Tissue Engineering:** Bioprinted structures using cell-laden hydrogels and photopolymerized bioinks have been shown to

yield promising results in both bone regeneration and soft tissue engineering.

- **Polymers, Composites, and Nanostructured Materials:** While polymers and composites offer low cost and rapid prototyping, nanotechnology-enhanced materials and biomimetic designs offer significant opportunities for next-generation biomedical solutions.

In general, AM technologies not only improve current manufacturing processes but also open up innovative horizons in areas such as antibacterial activity, tissue regeneration, and biocompatible material design. Future studies are expected to further strengthen the role of AM in medicine and health sciences by focusing on critical parameters such as biocompatibility, mechanical strength, biodegradability and sustainability.

### Credit authorship contribution statement

Cem Alparslan: Investigation, Visualization, Conceptualization, Software, Methodology, Writing-original draft. Şenol Bayraktar: Supervision, Conceptualization, Methodology, Investigation, Writing-review & editing.


### Ethical statement


Authors state that the research was conducted according to ethical standards.

## Data availability statement

No new data were created or analysed in this study.

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