Functionally Graded Additive Manufacturing for Orthopedic applications

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Abstract

Background: Additive Manufacturing due to its benefits in developing parts with complex geometries and shapes, has evolved as an alternate manufacturing process to develop implants with desired properties. The structure of human bones being anisotropic in nature is biologically functionally graded i,e. the structure possesses different properties in different directions. Therefore, various orthopedic implants such as knee, hip and other bone plates, if functionally graded can perform better. In this context, the development of functionally graded (FG) parts for orthopedic application with tailored anisotropic properties has become easier through the use of additive manufacturing (AM).

Objectives and Rationale: The current paper aims to study the various aspects of additively manufactured FG parts for orthopedic applications. It presents the details of various orthopedic implants such as knee, hip and other bone plates in a structured manner. A systematic literature review is conducted to study the various material and functional aspects of functionally graded parts for orthopedic applications. A section is also dedicated to discuss the mechanical properties of functionally graded parts.

Conclusion: The literature revealed that additive manufacturing can provide lot of opportunities for development of functionally graded orthopedic implants with improved properties and durability. Further, the effect of various FG parameters on the mechanical behaviour of these implants needs to be studied in detail. Also, with the advent of various AM technologies, the

functional grading can be achieved by various means e.g. density, porosity, microstructure, composition, etc. by varying the AM parameters. However, the current limitations of cost and material biocompatibility prevent the widespread exploitation of AM technologies for various orthopedic applications.

Keywords: ***Functionally Graded Parts; Additive Manufacturing; Orthopedics; Implants; 3D Printing; Medical Applications***

List of Abbreviations

AM	Additive Manufacturing
FGM	Functionally Graded Materials
FGAM	Functionally Graded Additive Manufacturing
CVD	Chemical Vapor Deposition
PEEK	Polyether Ether Ketone
PTFE	Poly-tetra-fluoro-ethylene
UHMWPE	Ultra High Molecular Weight Polyethylene
PMMA	Polymethyl Methacrylate
CFR	Carbon Fiber Reinforced
CNT	Carbon Nanotubes
LFA	Low Friction Arthroplasty
THA	Total Hip Arthroplasty
TKR	Total Knee Replacement
HNFSS	High-Nitrogen Nickel-Free Stainless Steel
PSI	Patient Specific Implants
EBM	Electron Beam Manufacturing
PVA	Polyvinyl Alcohol
PLA	Polylactic Acid
HLA	Hyaluronic Acid
FDM	Fused Deposition Modelling
SLM	Selective Laser Melting
SLS	Selective Laser Sintering
DED	Direct Energy Deposition
PCL	Polycaprolactone
TCP	Tricalcium phosphate
BCC	Body Centred Cubic
FEA	Finite Element Analysis

1. Introduction

Additive manufacturing (AM) is a layer-by-layer manufacturing technique, which creates the product into the final shape with accurate geometrical dimensions and minimal material wastage[1]. At present, AM is being widely used for medical, automotive, aerospace, and marine applications [2345678910]. In comparison to the conventional manufacturing, AM has the potential for developing complex geometries with ease of customization[11]. This application makes it the perfect contender in the medical sector, as the quick customization of implants and tools are very important for most medical (specifically orthopedic and dental) procedures [1213]. In recent years, the advancements in AM have led towards the development of tissues and organs, which will solve the donor shortage problem [141516].

Apart from these mentioned applications, AM is used to print the models for pre-operative surgical preparations that precisely depict the organ on which the surgery is to be performed. This has reduced surgery time and complexity of the procedure [17]. In orthopedics, stress shielding of implants is an important challenge faced by orthopedicians that is mainly due to the mismatch of mechanical properties between the implant and the bone, which can lead to implant failure. This issue occurs in conventionally manufactured implants as the properties such as porosity, strength; hardness cannot be patient specific and can become a cause for implant resorption. This problem can be better solved by additive manufacturing due to its control on mechanical and structural properties of implant that can alter the stress concentration, thus preventing stress shielding and failure of implant. Implant failure is also possible by improper torque on the screws and fixtures during the implantation [18]. Some fixtures used during orthopedic surgeries are bone screws, intramedullary rods, pins, wires, and spinal fixtures [19].

Out of the mentioned fixtures, bone screws are the most commonly used for fixing orthopedic fractures and implants. It is estimated that among the fractures that develop complications after implying fixtures, around 11% of the complications are due to screw-related issues [20]. In most cases, the stress shielding effect occurs between the bone and the screw that may cause severe pain and need surgical intervention. This issue has been solved by AM by developing patient-specific fixtures with optimized structure, which help in bone healing. However, the surface roughness associated with AM bone implants and fixtures can hamper bone regeneration, but biomechanical performance is enhanced [21]. Apart from the scientific point of view, AM has also proved itself to be cost-friendly. Due to reduced labor and tooling, the cost of implants has also been reduced significantly, indicating that it is the viable option in the present scenario for orthopedic applications[15]. The requirements for any orthopedic implant are given in figure 1.

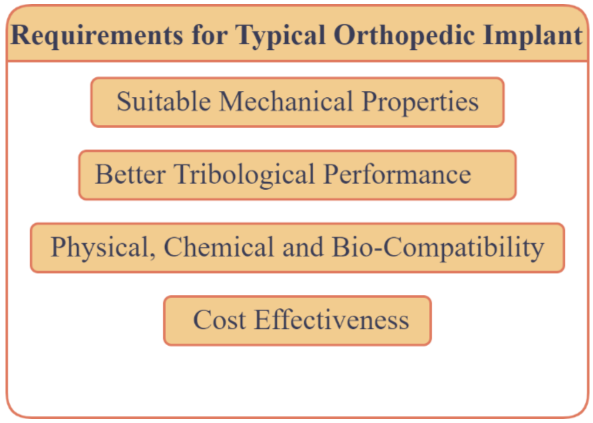

Figure 1: Requirements for any orthopedic implants

Bio-compatibility and wear resistance are the two most critical properties of implant materials [22]. In case of long term use of implants in a patient's body, biocompatibility plays a crucial role. Since most of the implant materials consist of metals, assessing their biocompatibility becomes important. Not all metals can be used as implant materials. Titanium and its alloys, stainless steel, magnesium alloys, chromium and cobalt based alloys have proven to exhibit high biocompatibility when used in implants [23]. They include materials like 316L stainless steel, Ti-6Al-4V, Ti-6Al-7Nb. In addition to good biocompatibility, Ti-6Al-4V provides excellent corrosion resistance as well owing to its capability to form an oxide layer on its surface upon exposure to oxygen environment, such as atmosphere[24]. Along with materials, various lubricants and synovial fluids have also been developed by researches to improve the biocompatibility of various implants[25].

The methodology adopted to develop this review paper has been based on searching various research databases by using various keywords related to the scope of the paper. Also, medical journals, reports and magazines have been consulted to compile this paper. The objectives of the paper include a) presenting a brief overview of the literature and basic concepts related to AM and FG b) representing a detailed discussion on how AM technologies can help to produce FG parts c) developing a discussion on how AM can help develop FG implants for orthopedic implants and present various material aspects. d) expressing a detailed literature related to mechanical aspects of FG Implants developed through AM.

1.2. Brief Background of Functional Grading

The concept of functionally grading of materials involves tailoring of their properties for specific requirements. It is defined as the gradual change in the composition or structure across the volume to attain the required set of properties for specific application areas [2627]. FGMs can be found in nature, bones, tissues of seashells, and plants like bamboo [282930]. It was Naotake who proposed the concept of functionally graded materials based on the observations made of naturally occurring materials or objects like teeth, bone etc. [31]. These mentioned natural objects or materials exhibit good mechanical or physical properties due to the graded structure along a certain direction that makes them perform better than the other materials [32]. FGMs are classified as continuous and discontinuous. In continuous FGMs the parameters like composition, microstructure, and temperature vary along a continuous curve, while in discontinuous FGMs vary in a discreet way (step wise) along the certain direction/length [33]. The cellular graded structures in FGM are capable of reducing or distributing the stress concentration in an object subjected to some external loading, Hence, enhancement in the mechanical and other physical properties are marked [34]. FGM objects find their application in aerospace, medical, electronics, and energy materials [35363738]. They are used for developing high temperature aerospace materials, which can exhibit excellent mechanical properties for high temperature applications. Bio-medical applications of FGMs are evolving at the larger scale from the couple of years. FGMs have been used to develop artificial bone and dental implants with good biomechanical compatibility [39]. The manufacturing process for FGM plays an important role in their working and exhibiting the desired properties. The conventional methods for manufacturing of FGM are liquid based (gel casting, centrifugal casting etc.), gas-based methods (CVD, PVD, Thermal Spray etc.) and solid phase powder method (powder metallurgy, spark plasma sintering) [354041424344]. The gas-based methods like CVD require heat, plasma or light as the source of energy. Gases like bromides, hydrides or chlorides are mostly used in gas-based methods. They require a lot of energy and characterized for the emission of toxic gases as the by-product. The liquid-based methods have the capability for mass production of FGM objects. Centrifugal casting is the most explored area of liquid based methods for functional grading but the gradient can be obtained only in the radial direction [45]. Similarly, in solid phase methods, the FGM objects show traces of pores, which can degrade the mechanical, thermal, structural properties of objects. Taking these problems in consideration, researchers are exploring FGM with AM and positive results have been observed so far. The Figure 2 gives the pictorial representation of various methods used for FGM.

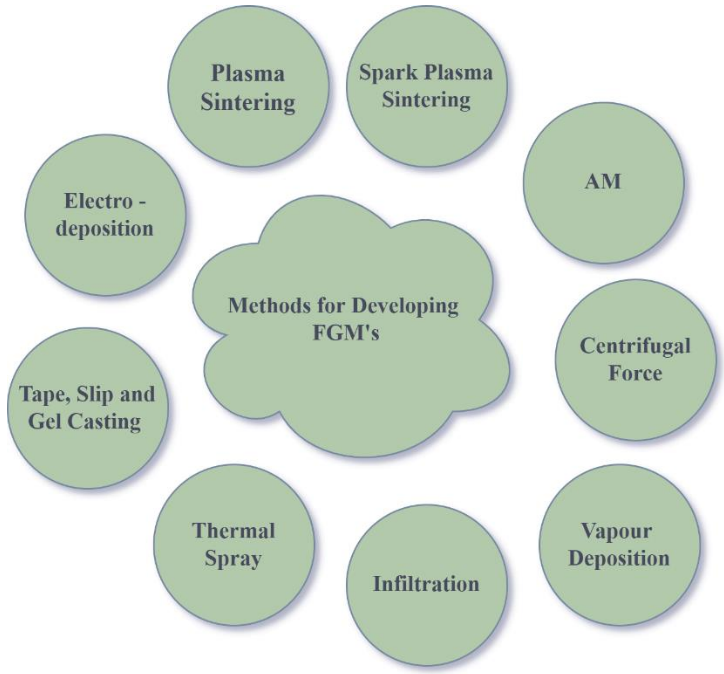

Figure 2: Methods for developing FGM's

1.3 Additive Manufacturing and Functional Grading

In comparison to conventional manufacturing, Researchers have found that AM is the better way to fabricate FGMs due to its extra-ordinary formability and optimized stress profiles in comparison to conventional manufacturing processes [33]. AM provides spatial and temporal control over the properties like microstructure which is not possible with conventional manufacturing processes. The FGM by AM has given rise to new domain called FGAM (Functionally Graded Additively Manufacturing). FGAM has the potential to develop and introduce compositional variation as well as microstructural variation in a material [46]. The FGAM is done in three ways; (1) Homogenous composition with gradual variation of other parameters like density, cellular lattices or structures and temperature. (2) Heterogeneous composition of material. (3) The combination of (1) and (2). The FGAM is performed in different stages, which involve modeling of structures at a macro as well as meso scale. Structural modelling entails the design of the full structure and the lattices inside it. Structural modelling is followed by material selection. The FGAM parameters like material density, pattern, temperature, layer thickness are altered with the slicer software available. Before going towards the actual printing, the model undergoes simulation. This provides an initial guess about the properties due to the selected structure or material. Once the structure, material and the grading methods are decided, the printing of FGAM product starts. The product undergoes various types of characterizations for quality and performance tests. At present, FGAM is in its infancy period. No doubt, a lot of research is going on in the field, but very less research is transferred to "Technological Readiness

Level”. The reason is very less simulation tools for complex FGAM process. The aim of this review is to provide the recent and important insights of FGAM and orthopedic research. A state of comparison is done between the various FGAM technologies for orthopedic implants, and critical analysis is performed to provide a better option for a specific orthopedic implant or tool. The various variables, which can help to attain the functionality in materials by AM, are shown in Figure 3.

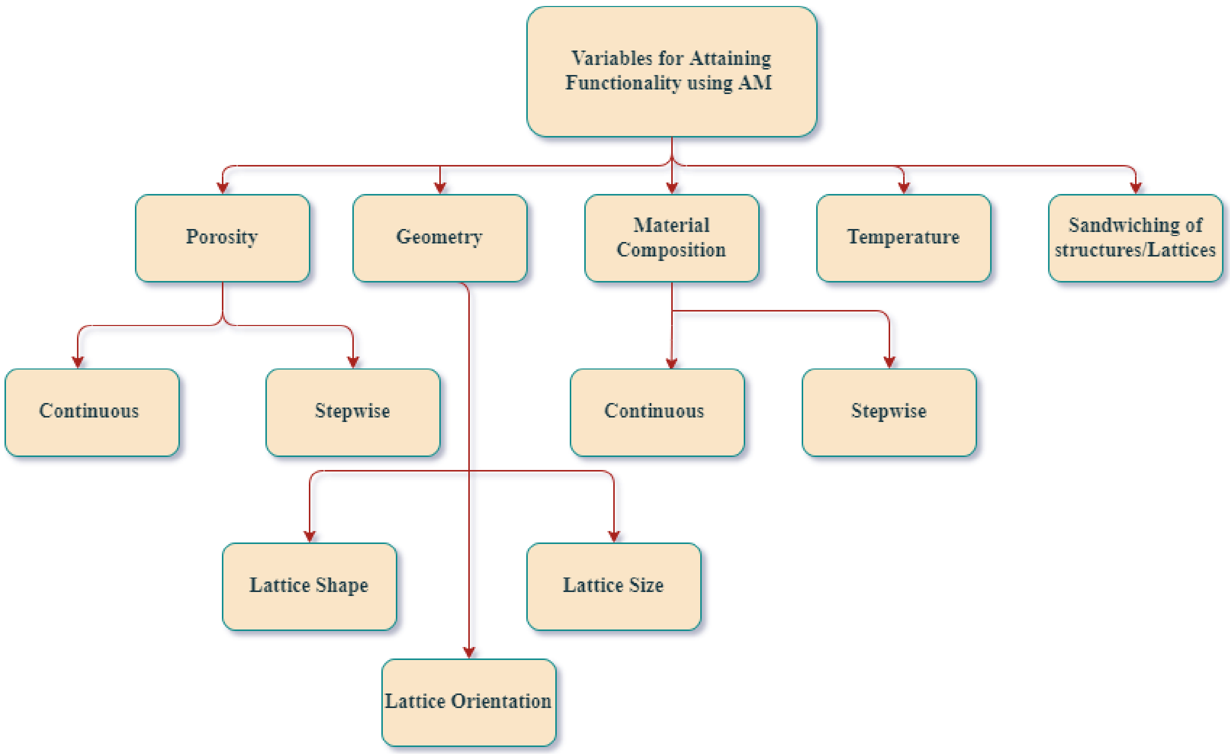

Figure 3: Variables for FGAM

2. Materials and Functional Aspects of Orthopedic Implants

The use of implants for orthopedic applications by started way back in 1895. Metallic plate was implanted at the fracture site for quick healing [47]. Since then, the researchers are constantly working to upgrade the implant technology for orthopedic applications. The era of modern screws for fracture treatment came in 1920 with the introduction of stainless steel as the bone screw material [48]. It proved to be corrosion resistant and biocompatible. Apart from stainless steel, Titanium alloys gained for orthopedic implants due to its durability and bio tolerance [49]. Nowadays, Austenitic chromium-nickel steel doped with molybdenum is widely used for joint implants [50]. Cr-Ni-Mo steels are characterized for low corrosive behavior. In addition, their mechanical properties can be altered according to need by cold working [51]. The main problems associated with orthopedic implants is the development of infections, allergies and pain. Also, some life threatening diseases like cancer or tumor can be the cause for implant removal [52]. The process of re-surgery for implant removal is hectic and may cause permanent side effects. Therefore, Researchers are working to develop biodegradable implants from metallic alloys, polymers and ceramics [53]. Magnesium when alloyed with some material to give better biodegradable implants for orthopedic applications [54]. Although the strength of biodegradable implants have less strength than the non-biodegradable materials but the biocompatibility is excellent [5556]. Among the polymeric materials PTFE, PEEK and UHMWPE are used for implants for hip replacements due to good stiffness and strength [57]. Ceramics have developed a unique identity for their biocompatibility and porous structure. They are widely used for orthopedic implants with flexible and high load carrying capacity. Some of the important ceramics used for orthopedic applications are: Alumina, Zirconia, Akermanite [58]. To avoid the re-surgeries, the selection of perfect non-biodegradable material for orthopedic implants is very important. The researchers are constantly trying to develop the mechanical and biodegradable materials for orthopedic implants, which are job specific and patient specific. This section summarizes the various materials used for different orthopedic implants. The detailed description of mechanical and biocompatibility in implants is provided.

2.1. Knee Implants

The knee consists of four types of bones: the Femur, Patella, Tibial and Fibula [59]. Knee replacement is considered one of the remarkable achievements to improve the quality of human life. Around 50000 knee transplants are done in a year at United States [57]. Cobalt-chromium (Co-Cr), SS 316L, NiTi alloy, and titanium (Ti) and its alloys are widely used for knee implants. For every knee implant, it is necessary that the material should have a low modulus of elasticity (15-30 GPa) to eliminate the stress shielding effect [6061]. In addition, the material should be ductile to avoid material failure due to brittle fracture [62]. Moreover, the strength and density of the material should be maintained as that of the real bone [63]. Figure 1 represents the various bones in knee joint and the femoral component of knee implant [64]. Earlier, knee implants were only made up of metals but with the development in the materials, the metals were replaced with alloys, ceramics and polymers [5765]. Patients with metal sensitivity can have problems with the metallic implants. In addition, the wear particles of polyethylene can be toxic to human body. To tackle these problems, researchers have developed coated implants with least wear possibility and no metal contacts [66]. The knee implants are categorized into four types: total knee replacement, kneecap implant, unicompartmental knee implant and revision knee implant [67]. The major components of total knee replacement implants are femoral and tibial components. The femoral part consists of a metal piece, which is attached with the femur end. The tibial component has the plastic spacer and metal piece inserted into the tibia [68]. Researchers have given pictorial representation shows the various components of total knee replacement implant[64]. The kneecap replacement is the replacement of patella. It is used to replace the worn out knee cap so that pain in the future is avoided.

The wide variety of biomaterials are used for knee implants. With an aim of developing new materials for knee implants, researchers are exploring a wide variety of materials. Apart from that, potential applications for materials with maximum stress shielding capacity, wear resistance and fatigue resistance are designed and explored. Some of the important work related to the knee implants and material observations are given in Table 1.

Table 1: Important work related to knee implant.

Material	Material Type	Observation	Author
PMMA	Polymer	Also referred as bone cement due to its stability and non-toxicity. It is used as spacer between tibia and femur.	[69]
UHMWPE	Polymer	Mostly used as inserts for tibial part. Wear resistance is enhanced by adding small amount of CNTs.	[70]
CFR-PEEK	Polymer	Better stress shielding effects and mechanical and tribological properties.	[71]
Titanium-aluminum-vanadium	Alloy	High density material used for tibial tray	[72]
Titanium-niobium nitride	Alloy	Material has high corrosion resistance and good biocompatibility.	[66]
Cobalt Chromium	Alloy	This material is mostly used for femoral component. It possess low stiffness.	[67]
Co-Cr-Mo	Alloy	High corrosion resistance and high toughness fatigue.	[73]
CuAlNi	Alloy	Good ductility and economical to use.	[65]
Zirconia	Ceramic	Used in femoral part. Better corrosion resistance	[74]

Alumina	Ceramic	Material has chemical inertness and flexural strength.	[74]

2.2. Hip Prosthesis

Hip is one of the important joints in our body as it is subjected to a heavy load of upper body and has the difficult task of joining pelvis with the femur. The head of the femur is smoothly fitted inside the spherical cavity of the acetabulum. The joint is enveloped in a ligament, which is responsible for its stability [75]. Osteoarthritis is one of the common problems that is associated with the hip joint in the older age. It is associated with a sharp pain due to the stiffness of the joint. Osteoarthritis causes permanent damage to the hip joint that is irreversible, and joint replacement is the only option. The surgical procedure to address such problem is total hip replacement also called the Total Hip Arthroplasty (THA). The various components involved in total hip replacement are given by Neira et al[76]. The history of THA goes back to 1840, the attempt to replace the acetabular and femoral heads with wooden blocks [77]. The results of this experiment were not good. The wear debris from the wood caused serious biological issues within the body. To maintain the compatibility issues various biomaterials were applied over the prosthesis, some of them are pig bladder, skin, gold foil etc. [78]. After a while, these biocompatible materials were replaced with sliver, zinc, rubber and wax [79].

The hip replacement surgery has various development phases. In the earlier days of this procedure, the rubber mainly made the femoral. In few years, it was replaced with the ivory nail [77]. Similarly, for the femoral cup, glass and bakelite were introduced [80]. With the introduction of stainless steel to the domain, the procedure became more popular and success rates were enhanced. The stainless steel material when used with the long-stemming element for femoral neck and femoral head gave good results [77]. The modern era for total hip replacement surgery started from 1960’s with onset of Low Friction Arthroplasty (LFA). The first model of LFA consisted of stem made up of stainless steel, Cup made up of PTFE and a femoral head with diameter of 22.2mm fixed with acrylic cement. PTFE showed some inflammatory signs therefore, it was replaced with UHMWPE [81]. With the passage of time, new material came into the existence whose biocompatibility are excellent, good mechanical strength and less weight. Some of the advanced materials for THA are in the table 2.

Table 2: Materials used for THA

Material	Material Type	Observation	Author
PTFE	Polymer	It showed thermal stability and bio-inertness but wear rate was high.	[82,83]
Glass Fiber Reinforced PTFE	Polymer	Poor tribological behavior and highly reactive with the skin, hence responsible for developing infections.	[84]
UHMWPE	Polymer	UHMWPE were sterilized with gamma radiations, which increased the oxidation and wear resistance. The crosslinking of UHMPE has shown reduction in mechanical properties.	[85,86]
PEEK	Polymer	Chemical Inertness and biocompatibility are in PEEK based hip implants. The mechanical properties are also relatively good.	[87]
Cobalt Chromium Molybdenum Alloys	Alloy	The cobalt chromium alloys are characterized for high stiffness; hence, patients are subjected to pain.	[88]
Stainless Steel	Alloy	These alloys show low strength and ductility. Therefore, they have been replaced with CoCrMo Alloys	[88]
Titanium Alloy	Alloy	Ti-6Al-4V is considered as the lightweight material with good mechanical properties, which is compatible for femoral stem.	[89,90,91,88]

		However, the problem arises with the vanadium. The vanadium is considered toxic therefore better compositions like Ti-5Al-2.5Fe and Ti-6Al-7Nb, which have better biocompatibility and enhanced modulus of elasticity.	
Alumina	Ceramics	It shows good tribological properties, but mechanical properties are not good. The initial level of alumina had problems like low density and weak microstructure. These problems were addressed by the modified version of alumina known as Biolox.	[92][93][94]
Zirconia	Ceramics	Zirconia exhibit excellent mechanical properties and resistance towards crack development. Y-TZP, newly developed zirconia has shown excellent wear properties, toughness, therefore used for THA.	[95]
Zirconia Toughened Alumina	Ceramics	With the addition of Zirconia, the toughness of alumina has enhanced. The clinical ZTA that has been used for THA is Biolex Delta.	[96]

2.3. Bone Plates and other Fixtures

Fracture is the most occurring phenomenon with the bones. To fix these fractures, researchers have developed a special kind of fixture known as bone plates that are the most found implants, used for internal fixation of bones [97]. For perfect bone plates, it is important for them to exhibit resistance towards various mechanical properties like tension, compression and bending [98]. Various surgical procedures that are taken into consideration for the installation of bone plates are open reduction and internal fixation and bridge fixation. Among the three procedures, the bridge fixation method is considered as least destructive methods for plate installation. Rest of the two damage the tissues and blood supply mechanism over that area. In addition, the surgical time for bridge fixation is less as compared to open reduction and internal fixation method [99]. To fix the fracture of patients with co-morbidities like cancer, diabetes, special care is to be taken during the surgery like least tissue damage and minimal wound for surgical procedure. Bone plate does not seem to be feasible for these kind of situations therefore intramedullary nails are to be employed for such tasks [100]. IN shows excellent torsional load bearing capacity with biomechanical stability [101]. They are characterized for steady ambulation and mobilization of joints. Apart from these bone plate and intramedullary nails, there are other fixtures like screws, nails, pin and wires, which are being used in orthopedic surgeries. Some prominent areas of application of these fixtures include provisional fixation and bone traction procedure [102]. The material details of these fixtures and plates is given in the table 3.

Table 3: Materials used for Fixtures and Plates

Fixture	Material	observation	Author
Plate	316L Austenitic Steel	316L Austenitic steel have been widely used for manufacturing of plates. The mechanical properties are good; however, the stress shielding comes into play due to its young's modulus that is much higher than the bone, which may slow down the healing process. The other problem related to the biocompatibility, since it contains nickel and chromium, which are considered toxic substances.	[103]
Plate	high-nitrogen nickel-free stainless steel (HNFSS)	Biocompatibility is extremely good. The strength high than the conventional 316L Austenitic steel. The bending and compression are also good.	[104]
Plate	Titanium Alloys	The widely used Ti-6Al-4V possess high biocompatibility issues due to Al and V and can cause long-term health issues.	[105]

		Also, the wear resistance isn't appreciable. Therefore, Al and V were replaced by β phase materials like Nb, Zr, Mo and Ta, which have better biocompatibility. The Titanium alloys have overall issues with poor wear and fatigue resistance for bone plate applications.	
Plate	Chromium Alloys	The chromium alloys are not considered as the perfect material for bone plates due to biocompatibility issues. Two common chromium alloys that are wrought Co-Ni-Cr-Mo alloy and cast Co-Cr-Mo are used for bone plates. They have similar wear resistance but differ in elastic moduli.	[105]
Bone Screw	Titanium Based Bio Materials	The biocompatible titanium alloys have been widely used for bone screws. They have low fatigue and wear resistance.	[106]
Bone Screws	Cobalt based alloys	The cobalt chrome have excellent mechanical properties. It has been widely used for bone screw development.	[107]

3. Orthopedic Implants and Additive Manufacturing

AM has vital role in the development of orthopedic implants. The ability for mass customization, high speed and accuracy has made it popular for the manufacturing of scaffolds, implants and other fixtures. The feature of patient specific implants and fixture by additive manufacturing have revolutionized the orthopedic sector. The development of strong porous implants with AM has helped in the ingrowth of bone, which is responsible for quick healing and enhance osseo-integration. In addition, the control over the porosity has helped in tibia graft fixation and improved the biomechanical performance bone and screw juncture [108]. In the present era, researchers are working for the development of smart implants, which help in early diagnosis of any problem occurring with the implant. They can help in minimizing the threat at an early hour and proper treatment is received [109]. The development of smart orthopedic implants with additive manufacturing have almost revolutionized the major problems associated hip prosthesis and knee joints also, more the technology has contributed a lot in bone healing assessment and loosening monitoring [110]. The conventional methods of implant manufacturing have lot of irregularities such as manufacturing complex shape and size, the least or no control over the porosity of the implant [111]. Since all these parameters, play an important role in bone regeneration and are addressed with the additive manufacturing technologies.

Improved and high quality healthcare is one of the main objectives of any society and new methods are being explored to achieve this. Additive manufacturing has proven to enhance the economic credibility of products by bringing down their final cost. In this context, AM has shown promising results in the field of orthopedics as well [112]. AM has always focused on personalized implants for patients and in such cases, economic analysis of the process is very critical. Further, the use of AM in orthopedics at a larger scale is restricted by the high cost of material, technology and skilled manpower related to AM particularly in developing economies. Therefore, the focus should be on making the part affordable so that it can benefit more numbers of patients. Even if the implant manufactured meets all the required service standards, a patient would not feel inclined to use it if it is not affordable. Hence, economic validation is important in such cases. The recent literature citing the importance of AM in orthopedics in given the table 4.

The Hip replacement surgery with the involvement of AM started with the development of surgical guides for total hip replacement surgery, specifically for cup replacement [113]. The results showed better results as compared with the conventional manufacturing. With the further development in the field, researchers developed 3D printed custom cages for THA. Total haris-hip score and radiography technique analyzed the results, which clearly showed stability in the fixation as compared to the conventional manufacturing [114]. The 3D printed acetabular cups, which are the key components in THA have also shown better “time to weight bear” ratios than the conventionally manufactured acetabular cups [115]. The feasibility for customization with AM has led to the development of patient specific acetabular components that are suffering with colossal cup damage [116]. Apart from acetabular cup, researchers have worked for 3D printed femoral neck and guides which proved efficient than the conventional manufacturing [117]. The AM technologies that is mostly associated with acetabular cup manufacturing is Powder bed fusion technique [114-116][118119120]. The first 3D printed acetabular component was developed in 2007 and after that, 3D printing technologies emerged as the biggest players in orthopedic applications [121]. At present, the maximum pore size of acetabular cup is in between 300–900 µm with porosity ranging from 50-90%. UK based company called Corin [121] designed it.

The Total Knee Replacement surgeries and implants associated with it have undergone a tremendous development with advent of patient specific implants (PSI) with 3D printing. Not implants, 3D printing has also brought revolution in guides and cutting blocks of TKR. Research for the development of patient specific tools as cutting blocks and guides have been reported [122123]. The quality of guides and blocks have improved but they are not cost effective. In the initial stages of AM in TKR, it worsened the condition of implants in patients [124125]. However, with the advancement in domain, it improved the quality and life span of implants [126]. The researchers have tried to improve the accuracy of neutral axis in TKR implants by keeping giving the emphasis on PSI's [127]. The TKR implants like femoral intramedullary rod showed less drainage but no significant improvement in the surgical time [128]. With the development of 3D printed osteotomy guide, the surgical time and blood loss have reduced significantly [129]. In addition, the 3D printed Cement less tibial base plate is considered as the success in terms of survival rate and post-surgery complications [130].

Bone screws and plates are the integral part of any orthopedic surgery where they are used for fixation. The fixators may be permanent or temporary. The most important part for any screw or plate is its biocompatibility and its strength. The porosity of screws and plates for bone-regeneration and its stability for bone to bone or bone to implant contact is very essential. As the AM applied, the porous screws and plates are obtained which can help in attaining the osseo-integration and vascularization, which is not possible with the conventional manufacturing [21]. In addition, the porosity enabled by AM in screws and plated can be a big contributor for bone tibia graft fixation with can improve the biomechanical performance of bone-tendon-screw interface [108]. Researchers have observed that 3D printed screws have better vascularization as compared to the conventionally manufactured screws [131]. Also, the bonding force in bone and the implant is reported for the 3D printed screws [132]. The lattice-printing pattern in AM helps in designing the implants, screws and plates with specific lattice structure, which can be useful in tailoring their mechanical properties. Researchers have designed AM cancellous screws inspired by auxetic lattice structures that provided extra stiffness and strength [133]. A similar kind of work was done for pedicles where the AM enabled auxetic structures helped in bone screw fixation by radial expansion that further helped in developing resistance against the pulling out under the tensile force [134]. Researchers have also evaluated the effect of infill pattern on the mechanical properties of cancellous screws. The shear strength of cancellous screws for 100% insertion depths is reported for honeycomb lattice while as modulus of toughness is maximum for rectilinear printing patter [135].

Table 4: Recent advances in AM and orthopedics

Implant/fixture	Material	AM Technique	Observation
Bone plate [136]	Tantalum (Ta) coated Ti6Al4V	Electron Beam Melting	The Tantalum is coated over TiAl4V using CVD process. This bone plate has shown similar elastic moduli as that of cortical bone hence stress shielding is avoided. Ta coated surface enhance

			the cell proliferation on the scaffolds. In addition to this, osseointegration and osteogenic qualities of scaffolds have enhanced as compared to simple bone plates.
Plastic Liner of Acetabular Component [137]	PLA	Fused Deposition Modelling	The surface roughness remains a problem although no inner defects have reported by the radiography.
Acetabular Cups [138]	Ti6Al4V	Electron Beam Manufacturing	The EBM manufactured cups were compared with the conventional ones and results showed that first ones were found of cavities while as the later ones were free from cavities.
Multi Material Knee Joint Model [139]	Agilus30 (FLX935), Tango (FLX930), and Digital ABS (RGD5130).	Polyjet Printing	This Knee joint is supposed to replace the conventionally manufactured knee joint for educational purposes. Further, the mechanical properties are sufficient to withstand the flexo-extention. The fiber matrix may replace other materials in the future course of time for mimicking soft tissues.
Scaffold Material for cartilage applications. [140]	PLA Coated with PVA and HLA fibers	FDM for printing and Hybrid electrospinning for coating on scaffolds	The developed scaffolds are non-toxic and hydrophilic in nature. The overall coating enables increase in the mechanical properties like tensile strength. Further, the failure strain is reduced.

4. Functionally Graded Orthopedic Implants with Additive Manufacturing

The aim of implementing FGM in orthopedics is to produce implants or fixtures, which have better mechanical and biological properties. The concept of FGM in orthopedics have enhanced the quality of implants. The challenges such as stress shielding and residual stresses on the surfaces of implant and joint are being addressed with FGM via AM. The functionally grading is usually achieved via varying material composition, altering the porosity and microstructure of material in a well-defined manner [141]. Researchers have recommended the use of FGM in the domain of orthopedics in order to avoid the use of functionally graded coatings that are more prone to peeling off and chemical instability [142]. Moreover, the methods for developing functionally graded coatings, such as plasma spray and chemical vapor deposition, are limited to small parts and consume a lot of energy [35]. Since AM is not limited to smaller parts, and because it is feasible for multi-material printing, it has a key role to play in the manufacturing of functionally graded orthopedic implants [143]. Porosity is an important parameter for orthopedic implants since bone regeneration depends on it. AM has the capability to develop functionally graded porous structures in which the porosity changes across the volume of the implant. The low porous portion of implant has good mechanical properties and high porous end has better fixation properties; hence, the bone ingrowth is possible [144]. AM techniques that are commonly used for FGM implants are powder-based fusion methods, like SLS and SLM. Apart from these methods, DED (Direct Energy Deposition) is also used, but certain limitations like material porosity cannot be controlled [145]. The FGM can surely help in better osseointegration and implant stability, which can contribute towards implant stability and hence prevent the implant loosening.

Functionally graded ortho-implants by means of porosity grading have been widely explored by researchers. Both numerical as well as experimental investigations have been performed. Researchers have developed functionally graded acetabular cups with SLM technology [146]. Here the porosity was graded in the octet-based lattice structure. The researchers also proposed increasing the strut diameter form outer to inner surface of the cup. It was analyzed that the model could sustain maximum stresses that occur in the day-to-day life. Researchers have also used the combination of porosity and material grading with the help of a DED-based manufacturing system for acetabular cups [147]. The results showed improved bone ingrowth due to the porous titanium alloy at the mating end. In addition, the wear rates were reduced due to cobalt alloy mating with the metallic part. This design also enhances the implant stability. Researchers have also addressed the porosity grading in axial as well as radial directions. Octahedron lattice structure was used for Co-Cr alloy with SLM process. This method of grading reduced stress-shielding effects, which in turn improved the implant stability [148]. Researchers have also worked on functionally graded 3D-printed femoral heads with polycaprolactone (PCL) and b-tricalcium phosphate (b-TCP). The grading in porosity affected the mechanical properties like compressive modulus. The scaffolds of lower porosity exhibited high compressive strength [149]. The control over the porosity and material concentration proved an efficient method for treating early stage osteonecrosis of femoral bone. Further, in the thirst for proper methodology for functionally graded additive manufacturing, researchers worked on scaffold manufacturing with dense in and dense out samples of Ti6Al4V for scaffold application [150]. SLM for BCC lattice structure manufacturing is used. The results of graded samples are compared with uniform lattices of strut diameters of 0.4, 0.6, and 0.8 mm. The compressive stress of FG samples was twice that of uniform samples. In addition, deformation in uniform samples was more abrupt than in FG samples. FG by means of varying the material concentration also has significant effect of the mechanical properties of implants. Researchers observed the effect of grading the volume percentage in Invar 36/TiC composite with varying concentrations of TiC from 0 to 50% with laser based manufacturing at the printing speed of 20mm/s. As the TiC % increases, mechanical properties like hardness and tensile strength also increases [151].

With the advancement in the fields of FGM and orthopedics, researchers came to know that to achieve the mechanical properties and fracture behavior of real bone, one must not rely on the porosity and material gradient. There are other parameters also, like strain distribution with multi-material, various hierarchical designs of printing patterns and basic unit cell of implant, which must be taken into the consideration. Mathematical models like Voxel approximation have been widely used by researchers. In order to achieve the proper combination for hard-soft (bone type) material, researchers used voxel-by-voxel multi-material 3D printing manufacturing using brick and mortar arrangement for higher fracture energies [152]. A new domain for cell modification optimization for scaffold application is emerging. In context of this idea, researchers worked on developing optimum cell that have better mechanical and biological importance. A modified face-centered cubic cell is proposed with spherical pores for scaffold applications [153]. The stiffness is tailored with porosities of different percentages and optimized cell shape and size. This model is examined with FEA and 3D printed for mechanical testing. The cell ingrowth and elastic modulus were enhanced as compared to the orthogonal cylindrical struts.

New mathematical approach (TPMS) helps in balancing the porosity in the overall volume of scaffolds by just changing the formula of TPMS. It helps in attaining the smooth transition in porosity-based FGM scaffolds [154]. It is also responsible for enhancing the higher energy absorption and reducing the shear failure among the porosity graded scaffolds [155]. In addition, a TPMS-based sigmoid function enabled smooth transition of properties in a FG porous material [156]. Researchers have also developed a semi-empirical formula that can be used to predict the mechanical behavior of TPMS based laser-manufacturing systems for scaffold applications [157]. New studies in the domain of FGAM and orthopedic involve topological optimization of the lattices and methods of FGM [158159160]. The FGAM enhances the microstructure and mechanical characteristics, which could be considered important for orthopedic applications. Also, the SEM analysis of various FGM composites have good layering and smooth transition from one material to other which may reduce brittle fractures for FGAM orthopedic implants [161]. In addition, the introduction of artificial intelligence and machine learning techniques can provide optimal grading methods of material, temperature, porosity, microstructure etc. for better mechanical and biological properties. The mechanical behavior of FGM biomaterials for orthopedic applications is given in the section below:

4.1. Mechanical Aspects of Functionally Graded Additively Manufactured Orthopedic Implants

Large bone fractures and deep injuries have remained a problem for orthopedics. Replacement of bones with new additively manufactured scaffold is the alternative to this problem, but to fulfill stress shielding criteria and biocompatibility, one has to develop PSI's for effective scaffolds, which have good mechanical load bearing capability and biocompatibility. All these innovations take place to avoid re-surgeries and make life easier for patients. In context of this, researchers have worked on scaffolds with biomaterials with porous cellular structures that exhibit good mechanical behavior throughout the structure [162162163]. A lot of work has been done to investigate the mechanical behavior of the AM manufactured cellular structures [164165]. Researchers are in search of new methods for maintaining the balance between porosity (for bone ingrowth) and mechanical properties (compressive strength). Therefore, to meet these demands, functionally graded porous biomaterials are proposed, where the combination of controlled and graded porosity helps in meeting the demands of bone-in growth and high stress regions for bearing the high loads [16616740]. Hence, to develop a model for understanding the correlation between the mechanical properties and design for porous functionally graded structures are of great importance. In this regard, researchers worked on tuning the morphological parameters like porosity and pore size by altering the strut diameter of the lattice cell [168]. The variation in strut diameter can be multi or uni-directional [169]. Here the relationship between the biomechanical response and strut diameter of the lattice is observed [170]. Other researchers investigated the impact of post heat treatments and lattice transition methods on the mechanical behavior of FGAM porous biomaterials [169150]. The results showed better strength and high-energy absorption with systematic distribution of porosity over the implants. Further, researchers started working on developing the hybrid grading method for bio implants where different types of unit cells were used in a single part [171172]. In this case, porosity, cell size and pore size are altered separately with more flexible and smooth transitions of mechanical properties. It is also observed by researchers that varying the strut diameter is the best option among all the parameters for enhancing the functionality (biomechanical) in FGAM implants for orthopedic applications [173].

5. Limitation of Additive Manufacturing for Orthopedic Applications

AM is currently growing at faster pace in the domain of orthopedics. Researchers are putting their efforts to develop efficient and reliable patient specific implants using additive manufacturing [174175176]. However, there are certain limitations associated with the mechanical strength of implants and scaffolds due to the layer-by-layer manufacturing [177]. The conventional additive manufacturing process have poor bionic issues, which can lead to the necrosis[177]. Therefore, to avoid such issues, researchers are looking for more sophisticated AM technologies. The use of AM for orthopedics needs expertise over the use of proper material for implant or scaffold development. The generation of free radicals from the photopolymerizable resins, which are uncured, may become the source of cancer due to the presence of free radicals [178]. Moreover, it needs skilled operators that must have the ability to check the bed level, infill parameters and material fed to the nozzle [179]. The time factor is also the important limitation of AM for orthopedic implants. In most of the cases, it takes around 24 hours to print any standard implant. In addition, the availability of materials required for bio printing is also limited. Due to all these limitations AM has been widely used in surgical preparations and least used for development of patient specific artificial bones.

6. Conclusions

In this paper, we have discussed the importance of FGMs with AM for orthopedics. FGM has enabled implants with better mechanical properties. The control over the porosity and material concentration makes it a perfect candidate for scaffolds and orthopedic surgical tools. The implementation of FGM has brought a revolution in the orthopedic sector. The thermal stresses among the implants have been lowered to a large extent. In addition, the wear rate among the FGM materials is also lower than the conventionally manufactured materials; this advantage helps in implants to avoid post-surgery complications. FGM parts possess better strength and the deformity among the parts is very small. The FGM with AM has extreme control over microstructure, thus different lattices are used for patient specific implants and tools, so not only small parts but also implants of higher dimensions are possible with AM [180]. The paper shall help orthopedic experts and AM scientists to work further to exploit the potential of AM technologies in developing implants and parts for orthopedic applications.

7. Future Recommendations

AM has opened a window for grading the parts in all the directions. Apart from these advantages, there are some challenges associated with it. The FGM is associated with high material processing costs. The energy optimization for FGAM must be a research area for future course of time. The surface quality of FGAM orthopedic implants is always a problem. Due to the accuracy factor associated with it, it is not possible to manufacture FGAM implants in a large quantity. Hence, bulk manufacturing is not possible for FGAM implants in the present situation. The numerical methods for FGAMs are the future research areas, which include developing mathematical model for FGMs and simulation for various AM processes [181]. Also, researchers need to put their focus on process optimization for developing perfect orthopedic implants. In-depth research is required for cost cutting, since FGAM implants are expensive. Moreover, research into its reliability for high stress concentration areas is necessary [182].

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References

1. Aziz R, Haq MIU, Raina A. Effect of surface texturing on friction behaviour of 3D printed polylactic acid (PLA). *Polym Test*. 2020;85:106434.

2. Calle MAG, Salmi M, Mazzariol LM, Alves M, Kujala P. Additive manufacturing of miniature marine structures for crashworthiness verification: Scaling technique and experimental tests. *Mar Struct*. 2020;72:102764.

3. Kestilä A, Nordling K, Miikkulainen V, et al. Towards space-grade 3D-printed, ALD-coated small satellite propulsion components for fluidics. *Addit Manuf*. 2018;22:31-37.

4. Delic M, Eyers DR. The effect of additive manufacturing adoption on supply chain flexibility and performance: An empirical analysis from the automotive industry. *Int J Prod Econ*. 2020;228:107689.

5. Kretzschmar N, Chekurov S, Salmi M, Tuomi J. Evaluating the readiness level of additively manufactured digital spare parts: An industrial perspective. *Appl Sci*. 2018;8(10):1837.

6. Gibson I, Srinath A. Simplifying medical additive manufacturing: Making the surgeon the designer. *Procedia Technol*. 2015;20:237-242.

7. Rouf S, Raina A, Irfan Ul Haq M, Naveed N, Jeganmohan S, Farzana Kichloo A. 3D Printed Parts and Mechanical Properties: Influencing Parameters, Sustainability Aspects, Global Market Scenario, Challenges and Applications. *Adv Ind Eng Polym Res*. Published online 2022. doi:https://doi.org/10.1016/j.aiepr.2022.02.001

8. Malik A, Haq MIU, Raina A, Gupta K. 3D printing towards implementing Industry 4.0: sustainability aspects, barriers and challenges. *Ind Robot Int J Robot Res Appl*. Published online 2022.

9. Jandyal A, Chaturvedi I, Wazir I, Raina A, Haq MIU. 3D printing--A review of processes, materials and applications in industry 4.0. *Sustain Oper Comput*. 2022;3:33-42.

10. Haq MIU, Khuroo S, Raina A, et al. 3D printing for development of medical equipment amidst coronavirus (COVID-19) pandemic—review and advancements. *Res Biomed Eng*. Published online 2020:1-11.

11. Naveed N. Investigate the effects of process parameters on material properties and microstructural changes of 3D-printed specimens using fused deposition modelling (FDM). *Mater Technol*.

Published online 2020:1-14.

12. Haq MIU, Raina A, Ghazali MJ, Javaid M, Haleem A. Potential of 3D Printing Technologies in Developing Applications of Polymeric Nanocomposites. In: *Tribology of Polymer and Polymer Composites for Industry 4.0*. Springer; 2021:193-210.

13. Pettersson AB V, Salmi M, Vallittu P, Serlo W, Tuomi J, Mäkitie AA. Main clinical use of additive manufacturing (three-dimensional printing) in Finland restricted to the head and neck area in 2016--2017. *Scand J Surg*. 2020;109(2):166-173.

14. Zadpoor AA, Malda J. Additive manufacturing of biomaterials, tissues, and organs. Published online 2017.

15. Bandyopadhyay A, Bose S, Das S. 3D printing of biomaterials. *MRS Bull*. 2015;40(2):108-115.

16. Noroozi R, Tatar F, Zolfagharian A, et al. Additively Manufactured Multi-Morphology Bone-like Porous Scaffolds: Experiments and Micro-Computed Tomography-Based Finite Element Modeling Approaches. *Int J Bioprinting*. 2022;8(3).

17. Maini L, Vaishya R, Lal H. Will 3D printing take away surgical planning from doctors? *J Clin Orthop \& Trauma*. 2018;9(3):193.

18. Jamil M, Rafique S, Khan AM, et al. Comprehensive analysis on orthopedic drilling: A state-of-the-art review. *Proc Inst Mech Eng Part H J Eng Med*. 2020;234(6):537-561.

19. Sharp JW, Kani KK, Gee A, Mulcahy H, Chew FS, Porrino J. Anterior cruciate ligament fixation devices: Expected imaging appearance and common complications. *Eur J Radiol*. 2018;99:17-27.

20. Panagiotopoulou VC, Varga P, Richards RG, Gueorguiev B, Giannoudis P V. Late screw-related complications in locking plating of proximal humerus fractures: a systematic review. *Injury*. 2019;50(12):2176-2195.

21. Agarwal R, Gupta V, Singh J. Additive manufacturing-based design approaches and challenges for orthopaedic bone screws: a state-of-the-art review. *J Brazilian Soc Mech Sci Eng*. 2022;44(1):1-25.

22. Singh S, Prakash C, Ramakrishna S. 3D printing of polyether-ether-ketone for biomedical applications. *Eur Polym J*. 2019;114:234-248.

23. Tan XP, Tan YJ, Chow CSL, Tor SB, Yeong WY. Metallic powder-bed based 3D printing of cellular scaffolds for orthopaedic implants: A state-of-the-art review on manufacturing,

topological design, mechanical properties and biocompatibility. *Mater Sci Eng C*. 2017;76:1328-1343.

24. Buciumeanu M, Almeida S, Bartolomeu F, et al. Ti6Al4V cellular structures impregnated with biomedical PEEK-new material design for improved tribological behavior. *Tribol Int*. 2018;119:157-164.

25. Smith AM, Fleming L, Wudebwe U, Bowen J, Grover LM. Development of a synovial fluid analogue with bio-relevant rheology for wear testing of orthopaedic implants. *J Mech Behav Biomed Mater*. 2014;32:177-184.

26. Yang N, Hu S, Ma D, Lu T, Li B. Nanoscale graphene disk: a natural functionally graded material--how is Fourier's law violated along radius direction of 2D disk. *Sci Rep*. 2015;5(1):1-8.

27. Loh GH, Pei E, Harrison D, Monzón MD. An overview of functionally graded additive manufacturing. *Addit Manuf*. 2018;23:34-44.

28. Wegst UGK, Bai H, Saiz E, Tomsia AP, Ritchie RO. Bioinspired structural materials. *Nat Mater*. 2015;14(1):23-36.

29. Eder M, Jungnikl K, Burgert I. A close-up view of wood structure and properties across a growth ring of Norway spruce (Picea abies [L] Karst.). *Trees*. 2009;23(1):79-84.

30. Shirzad M, Zolfagharian A, Matbouei A, Bodaghi M. Design, evaluation, and optimization of 3D printed truss scaffolds for bone tissue engineering. *J Mech Behav Biomed Mater*. 2021;120:104594.

31. Noda N. Thermal stresses in functionally graded materials. *J Therm Stress*. 1999;22(4-5):477-512.

32. Bohidar SK, Sharma R, Mishra PR. Functionally graded materials: A critical review. *Int J Res*. 2014;1(4):289-301.

33. Zhang C, Chen F, Huang Z, et al. Additive manufacturing of functionally graded materials: A review. *Mater Sci Eng A*. 2019;764:138209.

34. Pietrzak K, Kaliński D, Chmielewski M. Interlayer of Al2O3--Cr functionally graded material for reduction of thermal stresses in alumina--heat resisting steel joints. *J Eur Ceram Soc*. 2007;27(2-3):1281-1286.

35. Mahamood RM, Akinlabi ET, Shukla M, Pityana SL. Functionally graded material: an overview. Published online 2012.

36. Pompe W, Worch H, Epple M, et al. Functionally graded materials for biomedical applications. *Mater Sci Eng A*. 2003;362(1-2):40-60.

37. Malinina M, Sammi T, Gasik MM. Corrosion resistance of homogeneous and FGM coatings. In: *Materials Science Forum*. Vol 492. ; 2005:305-310.

38. Mueller E, Drašar Č, Schilz J, Kaysser WA. Functionally graded materials for sensor and energy applications. *Mater Sci Eng A*. 2003;362(1-2):17-39.

39. Watari F, Yokoyama A, Omori M, et al. Biocompatibility of materials and development to functionally graded implant for bio-medical application. *Compos Sci Technol*. 2004;64(6):893-908.

40. Naebe M, Shirvanimoghaddam K. Functionally graded materials: A review of fabrication and properties. *Appl Mater today*. 2016;5:223-245.

41. Groves JF, Wadley HNG. Functionally graded materials synthesis via low vacuum directed vapor deposition. *Compos Part B Eng*. 1997;28(1-2):57-69.

42. Kawase M, Tago T, Kurosawa M, Utsumi H, Hashimoto K. Chemical vapor infiltration and deposition to produce a silicon carbide--carbon functionally gradient material. *Chem Eng Sci*. 1999;54(15-16):3327-3334.

43. Khor KA, Gu YW. Effects of residual stress on the performance of plasma sprayed functionally graded ZrO2/NiCoCrAlY coatings. *Mater Sci Eng A*. 2000;277(1-2):64-76.

44. Stewart S, Ahmed R, Itsukaichi T. Contact fatigue failure evaluation of post-treated WC--NiCrBSi functionally graded thermal spray coatings. *Wear*. 2004;257(9-10):962-983.

45. Kieback B, Neubrand A, Riedel H. Processing techniques for functionally graded materials. *Mater Sci Eng A*. 2003;362(1-2):81-106.

46. Li Y, Feng Z, Hao L, et al. A review on functionally graded materials and structures via additive manufacturing: from multi-scale design to versatile functional properties. *Adv Mater Technol*. 2020;5(6):1900981.

47. Uhthoff HK, Poitras P, Backman DS. Internal plate fixation of fractures: short history and recent developments. *J Orthop Sci*. 2006;11(2):118-126.

48. Stahel PF, Alfonso NA, Henderson C, Baldini T. Introducing the “Bone-Screw-Fastener” for improved screw fixation in orthopedic surgery: a revolutionary paradigm shift? *Patient Saf Surg*.

2017;11(1):1-8.

49. Nowacki J, Dobrzański LA, Gustavo F. *Implanty Śródszpikowe w Osteosyntezie Kości Długich*. International OCSCO World Press; 2012.

50. Dobrzański LA. *Metaloznawstwo Opisowe Stopów Metali Nieżelaznych*. Wydawnictwo Politechniki Śl{\k{a}}skiej; 2008.

51. Dobrzański LA. Materiały inżynierskie i projektowanie materiałowe: podstawy nauki o materiałach i metaloznawstwo. Published online 2006.

52. Chandra G, Pandey A. Design approaches and challenges for biodegradable bone implants: a review. *Expert Rev Med Devices*. 2021;18(7):629-647.

53. Han H-S, Loffredo S, Jun I, et al. Current status and outlook on the clinical translation of biodegradable metals. *Mater Today*. 2019;23:57-71.

54. Chen Y, Xu Z, Smith C, Sankar J. Recent advances on the development of magnesium alloys for biodegradable implants. *Acta Biomater*. 2014;10(11):4561-4573.

55. Kamrani S, Fleck C. Biodegradable magnesium alloys as temporary orthopaedic implants: a review. *Biometals*. 2019;32(2):185-193.

56. Tian L, Tang N, Ngai T, et al. Hybrid fracture fixation systems developed for orthopaedic applications: A general review. *J Orthop Transl*. 2019;16:1-13.

57. Carr BC, Goswami T. Knee implants--Review of models and biomechanics. *Mater \& Des*. 2009;30(2):398-413.

58. Moghadasi K, Isa MSM, Ariffin MA, et al. A review on biomedical implant materials and the effect of friction stir based techniques on their mechanical and tribological properties. *J Mater Res Technol*. Published online 2022.

59. Kumar R, Dubey R, Singh S, et al. Multiple-Criteria Decision-Making and Sensitivity Analysis for selection of materials for knee implant femoral component. *Materials (Basel)*. 2021;14(8):2084.

60. Farag MM. *Materials and Process Selection for Engineering Design*. CRC Press; 2020.

61. Long M, Rack HJ. Titanium alloys in total joint replacement—a materials science perspective. *Biomaterials*. 1998;19(18):1621-1639.

62. Bahraminasab M, Jahan A. Material selection for femoral component of total knee replacement

using comprehensive VIKOR. *Mater \& Des*. 2011;32(8-9):4471-4477.

63. van den Heever D, Scheffer C, Erasmus P, Dillon E. Method for selection of femoral component in total knee arthroplasty (tka). *Australas Phys \& Eng Sci Med*. 2011;34(1):23-30.

64. Markopoulos AP, Galanis NI, Karkalos NE, Manolakos DE. Precision CNC machining of femoral component of knee implant: A case study. *Machines*. 2018;6(1):10.

65. Abitha H, Kavitha V, Gomathi B, Ramachandran B. A recent investigation on shape memory alloys and polymers based materials on bio artificial implants-hip and knee joint. *Mater Today Proc*. 2020;33:4458-4466.

66. Herbster M, Döring J, Nohava J, Lohmann CH, Halle T, Bertrand J. Retrieval study of commercially available knee implant coatings TiN, TiNbN and ZrN on TiAl6V4 and CoCr28Mo6. *J Mech Behav Biomed Mater*. 2020;112:104034.

67. Pande S, Dhatrak P. Recent developments and advancements in knee implants materials, manufacturing: A review. *Mater Today Proc*. 2021;46:756-762.

68. Boorla R, Prabeena T. Fabrication of patient specific knee implant by fused deposition modeling. *Mater Today Proc*. 2019;18:3638-3642.

69. Gautam A, Callejas MA, Acharyya A, Acharyya SG. Shape-memory-alloy-based smart knee spacer for total knee arthroplasty: 3D CAD modelling and a computational study. *Med Eng \& Phys*. 2018;55:43-51.

70. Saenz CL, McGrath MS, Marker DR, Seyler TM, Mont MA, Bonutti PM. Early failure of a unicompartmental knee arthroplasty design with an all-polyethylene tibial component. *Knee*. 2010;17(1):53-56.

71. Kang K-T, Son J, Kwon SK, Kwon O-R, Park J-H, Koh Y-G. Finite element analysis for the biomechanical effect of tibial insert materials in total knee arthroplasty. *Compos Struct*. 2018;201:141-150.

72. Crockarell Jr JR, Hicks JM, Schroeder RJ, Guyton JL, Harkess JW, Lavelle DG. Total knee arthroplasty with asymmetric femoral condyles and tibial tray. *J Arthroplasty*. 2010;25(1):108-113.

73. Grupp TM, Schilling C, Schwiesau J, Pfaff A, Altermann B, Mihalko WM. Tibial implant fixation behavior in total knee arthroplasty: a study with five different bone cements. *J Arthroplasty*.

2020;35(2):579-587.

74. Zietz C, Kluess D, Bergschmidt P, Haenle M, Mittelmeier W, Bader R. Tribological aspects of ceramics in total hip and knee arthroplasty. In: *Seminars in Arthroplasty*. Vol 22. ; 2011:258-263.

75. Merola M, Affatato S. Materials for hip prostheses: a review of wear and loading considerations. *Materials (Basel)*. 2019;12(3):495.

76. Neira-Rodado D, Ortiz-Barrios M, la Hoz-Escorcia D, et al. Smart product design process through the implementation of a fuzzy Kano-AHP-DEMATEL-QFD approach. *Appl Sci*. 2020;10(5):1792.

77. Pramanik S, Agarwal AK, Rai KN. Chronology of total hip joint replacement and materials development. *Trends Biomater \& Artif Organs*. 2005;19(1):15-26.

78. Knight SR, Aujla R, Biswas SP. Total Hip Arthroplasty-over 100 years of operative history. *Orthop Rev (Pavia)*. 2011;3(2).

79. Gomez PF, Morcuende JA. Early attempts at hip arthroplasty: 1700s to 1950s. *Iowa Orthop J*. 2005;25:25.

80. Hernigou P. Smith--Petersen and early development of hip arthroplasty. *Int Orthop*. 2014;38(1):193-198.

81. McKee GK. Total hip replacement—past, present and future. *Biomaterials*. 1982;3(3):130-135.

82. Ramakrishna S, Ramalingam M, Kumar TSS, Soboyejo WO. *Biomaterials: A Nano Approach*. CRC press; 2016.

83. Sinha RK. *Revision of the Femoral Component*. Marcel Dekker, New York, NY, USA; 2002.

84. Schreiber A, Huggler AH, Dietschi C, Jacob H. Complications After Joint Replacement—Longterm Follow-Up, Clinical Findings, and Biomechanical Research. In: *Engineering in Medicine*. Springer; 1976:187-202.

85. Kurtz SM. *UHMWPE Biomaterials Handbook: Ultra High Molecular Weight Polyethylene in Total Joint Replacement and Medical Devices*. Academic Press; 2009.

86. Muratoglu OK, Bragdon CR, O'Connor DO, et al. Unified wear model for highly crosslinked ultra-high molecular weight polyethylenes (UHMWPE). *Biomaterials*. 1999;20(16):1463-1470.

87. Wang A, Lin R, Polineni VK, Essner A, Stark C, Dumbleton JH. Carbon fiber reinforced polyether ether ketone composite as a bearing surface for total hip replacement. *Tribol Int*.

1998;31(11):661-667.

88. Al Zoubi NF, Tarlochan F, Mehboob H, Jarrar F. Design of Titanium Alloy Femoral Stem Cellular Structure for Stress Shielding and Stem Stability: Computational Analysis. *Appl Sci*. 2022;12(3):1548.

89. Niinomi M. Mechanical biocompatibilities of titanium alloys for biomedical applications. *J Mech Behav Biomed Mater*. 2008;1(1):30-42.

90. Niinomi M. Recent metallic materials for biomedical applications. *Metall Mater Trans A*. 2002;33(3):477-486.

91. Stimac JD, Boles J, Parkes N, Della Valle AG, Boettner F, Westrich GH. Revision total hip arthroplasty with modular femoral stems. *J Arthroplasty*. 2014;29(11):2167-2170.

92. Hamadouche M, Sedel L. Ceramics in orthopaedics. *J Bone Joint Surg Br*. 2000;82(8):1095-1099.

93. Piconi C, Maccauro G, Muratori F, Del Prever EB. Alumina and zirconia ceramics in joint replacements. *J Appl Biomater Biomech*. 2003;1(1):19-32.

94. Willmann G. Ceramics for total hip replacement-what a surgeon should know. *Orthopedics*. 1998;21(2):173-177.

95. Kelly JR, Denry I. Stabilized zirconia as a structural ceramic: an overview. *Dent Mater*. 2008;24(3):289-298.

96. Gadow R, Kern F. Novel zirconia--alumina nanocomposites combining high strength and toughness. *Adv Eng Mater*. 2010;12(12):1220-1223.

97. Pater TJ, Grindel SI, Schmeling GJ, Wang M. Stability of unicortical locked fixation versus bicortical non-locked fixation for forearm fractures. *Bone Res*. 2014;2(1):1-5.

98. Nourisa J, Rouhi G. Biomechanical evaluation of intramedullary nail and bone plate for the fixation of distal metaphyseal fractures. *J Mech Behav Biomed Mater*. 2016;56:34-44.

99. Richard RD, Kubiak E, Horwitz DS. Techniques for the surgical treatment of distal tibia fractures. Orthop Clin N Am 45: 295--312. Published online 2014.

100. Wukich DK, Joseph A, Ryan M, Ramirez C, Irrgang JJ. Outcomes of ankle fractures in patients with uncomplicated versus complicated diabetes. *Foot \& Ankle Int*. 2011;32(2):120-130.

101. Ban I, Birkelund L, Palm H, Brix M, Troelsen A. Circumferential wires as a supplement to

intramedullary nailing in unstable trochanteric hip fractures: 4 reoperations in 60 patients followed for 1 year. *Acta Orthop*. 2012;83(3):240-243.

102. Takigami H, Sakano H, Saito T. Internal fixation with the low profile plate system compared with Kirschner wire fixation: clinical results of treatment for metacarpal and phalangeal fractures. *Hand Surg*. 2010;15(01):1-6.

103. Ganesh VK, Ramakrishna K, Ghista DN. Biomechanics of bone-fracture fixation by stiffness-graded plates in comparison with stainless-steel plates. *Biomed Eng Online*. 2005;4(1):1-15.

104. REN Y, ZHAO H, YANG K. Study on Lightweight Design and Biomechanical Property of High Nitrogen Nickel Free Stainless Steel Plate: Effect of Thickness Thinning. *Acta Met Sin*. 2017;53(10):1331-1336.

105. LI JL Q, YANG K, others. Materials evolution of bone plates for internal fixation of bone fractures: A review [J]. *J Mater Sci \& Technol*. 2020;36:190-208.

106. Zindani D, Kumar K, Davim JP. Metallic biomaterials—A review. *Mech Behav Biomater*. Published online 2019:83-99.

107. Diomidis N. Wear phenomena of metal joints. In: *Wear of Orthopaedic Implants and Artificial Joints*. Elsevier; 2013:246-277.

108. Huang Y-M, Huang C-C, Tsai P-I, et al. Three-dimensional printed porous titanium screw with bioactive surface modification for bone--tendon healing: a rabbit animal model. *Int J Mol Sci*. 2020;21(10):3628.

109. Li B, Zhang M, Lu Q, et al. Application and Development of Modern 3D Printing Technology in the Field of Orthopedics. *Biomed Res Int*. 2022;2022.

110. Ledet EH, Liddle B, Kradinova K, Harper S. Smart implants in orthopedic surgery, improving patient outcomes: a review. *Innov Entrep Heal*. 2018;5:41.

111. Kühne J-H, Bartl R, Frisch B, Hammer C, Jansson V, Zimmer M. Bone formation in coralline hydroxyapatite: effects of pore size studied in rabbits. *Acta Orthop Scand*. 1994;65(3):246-252.

112. Thompson MK, Moroni G, Vaneker T, et al. Design for Additive Manufacturing: Trends, opportunities, considerations, and constraints. *CIRP Ann*. 2016;65(2):737-760.

113. Hananouchi T, Saito M, Koyama T, Sugano N, Yoshikawa H. Tailor-made surgical guide reduces incidence of outliers of cup placement. *Clin Orthop Relat Res*. 2010;468(4):1088-1095.

114. Li H, Qu X, Mao Y, Dai K, Zhu Z. Custom acetabular cages offer stable fixation and improved hip scores for revision THA with severe bone defects. *Clin Orthop Relat Res*. 2016;474(3):731-740.

115. Wang S, Wang L, Liu Y, et al. 3D printing technology used in severe hip deformity. *Exp Ther Med*. 2017;14(3):2595-2599.

116. Citak M, Kochsiek L, Gehrke T, Haasper C, Suero EM, Mau H. Preliminary results of a 3D-printed acetabular component in the management of extensive defects. *Hip Int*. 2018;28(3):266-271.

117. Schneider AK, Pierrepont JW, Hawdon G, McMahon S. Clinical accuracy of a patient-specific femoral osteotomy guide in minimally-invasive posterior hip arthroplasty. *Hip Int*. 2018;28(6):636-641.

118. Vaithilingam J, Prina E, Goodridge RD, et al. Surface chemistry of Ti6Al4V components fabricated using selective laser melting for biomedical applications. *Mater Sci Eng C*. 2016;67:294-303.

119. Murr LE, Gaytan SM, Martinez E, Medina F, Wicker RB. Next generation orthopaedic implants by additive manufacturing using electron beam melting. *Int J Biomater*. 2012;2012.

120. Heinl P, Müller L, Körner C, Singer RF, Müller FA. Cellular Ti--6Al--4V structures with interconnected macro porosity for bone implants fabricated by selective electron beam melting. *Acta Biomater*. 2008;4(5):1536-1544.

121. Dall'Ava L, Hothi H, Di Laura A, Henckel J, Hart A. 3D printed acetabular cups for total hip arthroplasty: a review article. *Metals (Basel)*. 2019;9(7):729.

122. Nunley RM, Ellison BS, Ruh EL, et al. Are patient-specific cutting blocks cost-effective for total knee arthroplasty? *Clin Orthop Relat Res*. 2012;470(3):889-894.

123. Victor J, Dujardin J, Vandenneucker H, Arnout N, Bellemans J. Patient-specific guides do not improve accuracy in total knee arthroplasty: a prospective randomized controlled trial. *Clin Orthop Relat Res*. 2014;472(1):263-271.

124. Lustig S, Scholes CJ, Oussedik SI, Kinzel V, Coolican MRJ, Parker DA. Unsatisfactory accuracy as determined by computer navigation of VISIONAIRE patient-specific instrumentation for total knee arthroplasty. *J Arthroplasty*. 2013;28(3):469-473.

125. Stronach BM, Pelt CE, Erickson JA, Peters CL. Patient-specific instrumentation in total knee

arthroplasty provides no improvement in component alignment. *J Arthroplasty*. 2014;29(9):1705-1708.

126. Qiu B, Liu F, Tang B, et al. Clinical study of 3D imaging and 3D printing technique for patient-specific instrumentation in total knee arthroplasty. *J Knee Surg*. 2017;30(08):822-828.

127. Levengood GA, Dupee J. Accuracy of coronal plane mechanical alignment in a customized, individually made total knee replacement with patient-specific instrumentation. *J Knee Surg*. 2018;31(08):792-796.

128. Tian H, Zhao M-W, Geng X, Zhou Q-Y, Li Y. Patient-specific instruments based on knee joint computed tomography and full-length lower extremity radiography in total knee replacement. *Chin Med J (Engl)*. 2018;131(05):583-587.

129. Shen Z, Wang H, Duan Y, Wang J, Wang F. Application of 3D printed osteotomy guide plate-assisted total knee arthroplasty in treatment of valgus knee deformity. *J Orthop Surg Res*. 2019;14(1):1-7.

130. Sultan AA, Mahmood B, Samuel LT, et al. Cementless 3D printed highly porous titanium-coated baseplate total knee arthroplasty: survivorship and outcomes at 2-year minimum follow-up. *J Knee Surg*. 2020;33(03):279-283.

131. Dhandapani R, Krishnan PD, Zennifer A, et al. Additive manufacturing of biodegradable porous orthopaedic screw. *Bioact Mater*. 2020;5(3):458-467.

132. Lee B-S, Lee H-J, Lee K-S, Kim HG, Kim G-H, Lee C-W. Enhanced osseointegration of Ti6Al4V ELI screws built-up by electron beam additive manufacturing: An experimental study in rabbits. *Appl Surf Sci*. 2020;508:145160.

133. Yao Y, Wang L, Li J, Tian S, Zhang M, Fan Y. A novel auxetic structure based bone screw design: Tensile mechanical characterization and pullout fixation strength evaluation. *Mater \& Des*. 2020;188:108424.

134. Yao Y, Yuan H, Huang H, Liu J, Wang L, Fan Y. Biomechanical design and analysis of auxetic pedicle screw to resist loosening. *Comput Biol Med*. 2021;133:104386.

135. Karakurt I, Lin L. 3D printing technologies: techniques, materials, and post-processing. *Curr Opin Chem Eng*. 2020;28:134-143.

136. Liu B, Ma Z, Li J, et al. Experimental study of a 3D printed permanent implantable porous Ta-

coated bone plate for fracture fixation. *Bioact Mater*. 2022;10:269-280.

137. Sofia J, Ethiraj N, Nikolova MP. PRELIMINARY STUDY ON ADDITIVELY MANUFACTURED PLASTIC LINER OF AN ACETABULAR CUP COMPONENT. *J Teknol*. 2022;84(2):113-120.

138. Hothi H, Dall'Ava L, Henckel J, et al. Evidence of structural cavities in 3D printed acetabular cups for total hip arthroplasty. *J Biomed Mater Res Part B Appl Biomater*. 2020;108(5):1779-1789.

139. Ruiz OG, Dhaher Y. Multi-color and Multi-Material 3D Printing of Knee Joint models. *3D Print Med*. 2021;7(1):1-16.

140. Farsi M, Asefnejad A, Baharifar H. A hyaluronic acid/PVA electrospun coating on 3D printed PLA scaffold for orthopedic application. *Prog Biomater*. Published online 2022:1-11.

141. Mahamood RM, Akinlabi ET. Additive manufacturing of funtionally graded materials. In: *Functionally Graded Materials*. Springer; 2017:47-68.

142. Kumar RR, Wang M. Functionally graded bioactive coatings of hydroxyapatite/titanium oxide composite system. *Mater Lett*. 2002;55(3):133-137.

143. Mahmoud D, Elbestawi MA. Lattice structures and functionally graded materials applications in additive manufacturing of orthopedic implants: a review. *J Manuf Mater Process*. 2017;1(2):13.

144. Boccaccio A, Uva AE, Fiorentino M, Mori G, Monno G. Geometry design optimization of functionally graded scaffolds for bone tissue engineering: A mechanobiological approach. *PLoS One*. 2016;11(1):e0146935.

145. Krishna BV, Bose S, Bandyopadhyay A. Low stiffness porous Ti structures for load-bearing implants. *Acta Biomater*. 2007;3(6):997-1006.

146. Wang HV, Johnston SR, Rosen DW. Design of a graded cellular structure for an acetabular hip replacement component. In: *2006 International Solid Freeform Fabrication Symposium*. ; 2006.

147. España FA, Balla VK, Bose S, Bandyopadhyay A. Design and fabrication of CoCrMo alloy based novel structures for load bearing implants using laser engineered net shaping. *Mater Sci Eng C*. 2010;30(1):50-57.

148. Limmahakhun S, Oloyede A, Chantarapanich N, et al. Alternative designs of load- sharing cobalt chromium graded femoral stems. *Mater Today Commun*. 2017;12:1-10.

149. Kawai T, Shanjani Y, Fazeli S, et al. Customized, degradable, functionally graded scaffold for potential treatment of early stage osteonecrosis of the femoral head. *J Orthop Res*. 2018;36(3):1002-1011.

150. Onal E, Frith JE, Jurg M, Wu X, Molotnikov A. Mechanical properties and in vitro behavior of additively manufactured and functionally graded Ti6Al4V porous scaffolds. *Metals (Basel)*. 2018;8(4):200.

151. Li XC, Stampfl J, Prinz FB. Mechanical and thermal expansion behavior of laser deposited metal matrix composites of Invar and TiC. *Mater Sci Eng A*. 2000;282(1-2):86-90.

152. Mirzaali MJ, Cruz Sald\'\ivar M, de la Nava A, et al. Multi-material 3D printing of functionally graded hierarchical soft--hard composites. *Adv Eng Mater*. 2020;22(7):1901142.

153. Foroughi AH, Razavi MJ. Shape optimization of orthopedic porous scaffolds to enhance mechanical performance. *J Mech Behav Biomed Mater*. 2022;128:105098.

154. Montazerian H, Mohamed MGA, Montazeri MM, et al. Permeability and mechanical properties of gradient porous PDMS scaffolds fabricated by 3D-printed sacrificial templates designed with minimal surfaces. *Acta Biomater*. 2019;96:149-160.

155. Zhao M, Zhang DZ, Liu F, Li Z, Ma Z, Ren Z. Mechanical and energy absorption characteristics of additively manufactured functionally graded sheet lattice structures with minimal surfaces. *Int J Mech Sci*. 2020;167:105262.

156. Zhang X-Y, Fang G, Xing L-L, Liu W, Zhou J. Effect of porosity variation strategy on the performance of functionally graded Ti-6Al-4V scaffolds for bone tissue engineering. *Mater \& Des*. 2018;157:523-538.

157. Xiong Y, Han Z, Qin J, et al. Effects of porosity gradient pattern on mechanical performance of additive manufactured Ti-6Al-4V functionally graded porous structure. *Mater \& Des*. 2021;208:109911.

158. Liu Z, Gong H, Gao J, Liu L. Topological design, mechanical responses and mass transport characteristics of high strength-high permeability TPMS-based scaffolds. *Int J Mech Sci*. 2022;217:107023.

159. Whenish R, Velu R, Anand Kumar S, Ramprasath LS. Additive Manufacturing Technologies for Biomedical Implants Using Functional Biocomposites. In: *High-Performance Composite Structures*. Springer; 2022:25-44.

160. Lv Y, Liu G, Wang B, et al. Pore Strategy Design of A Novel Niti-Nb Biomedical Porous Scaffold Based on Triply Periodic Minimal Surface.

161. Kuffner BHB, Capellato P, Ribeiro LMS, Sachs D, Silva G. Production and Characterization of a 316L Stainless Steel/$β$-TCP Biocomposite Using the Functionally Graded Materials (FGMs) Technique for Dental and Orthopedic Applications. *Metals (Basel)*. 2021;11(12):1923.

162. Cheah CM, Chua CK, Leong KF, Chua SW. Development of a tissue engineering scaffold structure library for rapid prototyping. Part 1: investigation and classification. *Int J Adv Manuf Technol*. 2003;21(4):291-301.

163. Zok FW, Latture RM, Begley MR. Periodic truss structures. *J Mech Phys Solids*. 2016;96:184-203.

164. Gibson LJ, Ashby MF. Cellular Solids: Structure and Properties, Cambridge Univ. Published online 1999.

165. Hedayati R, Ahmadi SM, Lietaert K, et al. Isolated and modulated effects of topology and material type on the mechanical properties of additively manufactured porous biomaterials. *J Mech Behav Biomed Mater*. 2018;79:254-263.

166. Zhao S, Li SJ, Wang SG, et al. Compressive and fatigue behavior of functionally graded Ti-6Al-4V meshes fabricated by electron beam melting. *Acta Mater*. 2018;150:1-15.

167. Derby B. Printing and prototyping of tissues and scaffolds. *Science (80-)*. 2012;338(6109):921-926.

168. Han C, Li Y, Wang Q, et al. Continuous functionally graded porous titanium scaffolds manufactured by selective laser melting for bone implants. *J Mech Behav Biomed Mater*. 2018;80:119-127.

169. Maskery I, Aboulkhair NT, Aremu AO, et al. A mechanical property evaluation of graded density Al-Si10-Mg lattice structures manufactured by selective laser melting. *Mater Sci Eng A*. 2016;670:264-274.

170. Van Grunsven W, Hernandez-Nava E, Reilly GC, Goodall R. Fabrication and mechanical characterisation of titanium lattices with graded porosity. *Metals (Basel)*. 2014;4(3):401-409.

171. Yang N, Du C, Wang S, Yang Y, Zhang C. Mathematically defined gradient porous materials. *Mater Lett*. 2016;173:136-140.

172. Surmeneva MA, Surmenev RA, Chudinova EA, et al. Fabrication of multiple-layered gradient cellular metal scaffold via electron beam melting for segmental bone reconstruction. *Mater \& Des*. 2017;133:195-204.

173. Zhang X-Y, Fang G, Leeflang S, Zadpoor AA, Zhou J. Topological design, permeability and mechanical behavior of additively manufactured functionally graded porous metallic biomaterials. *Acta Biomater*. 2019;84:437-452.

174. Wong KC. 3D-printed patient-specific applications in orthopedics. *Orthop Res Rev*. 2016;8:57.

175. Wong TM, Jin J, Lau TW, et al. The use of three-dimensional printing technology in orthopaedic surgery: a review. *J Orthop Surg*. 2017;25(1):2309499016684077.

176. Verma T, Sharma A, Sharma A, Maini L. Customized iliac prosthesis for reconstruction in giant cell tumour: a unique treatment approach. *J Clin Orthop trauma*. 2016;7:35-40.

177. Javaid M, Haleem A. Additive manufacturing applications in orthopaedics: a review. *J Clin Orthop trauma*. 2018;9(3):202-206.

178. Okafor-Muo OL, Hassanin H, Kayyali R, ElShaer A. 3D printing of solid oral dosage forms: numerous challenges with unique opportunities. *J Pharm Sci*. 2020;109(12):3535-3550.

179. Ariz A, Tasneem I, Bharti D, et al. Is additive manufacturing of patient-specific implant is beneficial for orthopedics. *Apollo Med*. 2021;18(1):33.

180. Saleh B, Jiang J, Fathi R, et al. 30 Years of functionally graded materials: An overview of manufacturing methods, Applications and Future Challenges. *Compos Part B Eng*. 2020;201:108376.

181. Moita JS, Araújo AL, Correia VF, Soares CMM, Herskovits J. Material distribution and sizing optimization of functionally graded plate-shell structures. *Compos Part B Eng*. 2018;142:263-272.

182. Wu D, Liu A, Huang Y, Huang Y, Pi Y, Gao W. Mathematical programming approach for uncertain linear elastic analysis of functionally graded porous structures with interval parameters. *Compos Part B Eng*. 2018;152:282-291.