Research progress and clinical translation of three-dimensional printed porous tantalum in orthopaedics

*Jiawei Ying, Haiyu Yu, Liangliang Cheng, Junlei Li, Bin Wu, Liqun Song, Pinqiao Yi, Haiyao Wang, Lingpeng Liu, Dewei Zhao**

Key Words:
3D printed; additive manufacturing; orthopaedic implant; porous; tantalum

From the Contents

Introduction	166
Physical and Chemical Characteristics of Tantalum	167
Porous Structure of Tantalum	167
Three-Dimensional Printed Porous Tantalum	168
Mechanical Characteristics of Porous Tantalum	168
In Vitro Biological Characteristics of Porous Tantalum	169
Preclinical Experiments using Tantalum	171
Drug Delivery of Porous Tantalum	172
Clinical Translation of Porous Tantalum	173
Summary	175

ABSTRACT

With continuous developments in additive manufacturing technology, tantalum (Ta) metal has been manufactured into orthopaedic implants with a variety of forms, properties and uses by three-dimensional printing. Based on extensive research in recent years, the design, processing and performance aspects of this new orthopaedic implant material have been greatly improved. Besides the bionic porous structure and mechanical characteristics that are similar to human bone tissue, porous tantalum is considered to be a viable bone repair material due to its outstanding corrosion resistance, biocompatibility, bone integration and bone conductivity. Numerous in vitro, in vivo, and clinical studies have been carried out in order to analyse the safety and efficacy of these implants in orthopaedic applications. This study reviews the most recent advances in manufacturing, characteristics and clinical application of porous tantalum materials.

***Corresponding author:**
Dewei Zhao,
zhaodewei2016@163.com.

http://doi.org/10.12336/biomatertransl.2023.03.005

How to cite this article:
Ying, J.; Yu, H.; Cheng, L.; Li, J.; Wu, B.; Song, L.; Yi, P.; Wang, H.; Liu, L.; Zhao D. Research progress and clinical translation of three-dimensional printed porous tantalum in orthopaedics. *Biomater Transl.* **2023**, *4*(3), 166-179.

Introduction

Injuries to the musculoskeletal system are mainly caused by trauma or bone disease. Bone defects are an especially common clinical problem, resulting in significantly-reduced quality of life for millions of patients every year. Although autologous or allogeneic bone transplantation can partially repair bone defects, there are problems such as source limitation, and risks of donor site complications and infectious diseases. Therefore, finding more suitable bone substitute materials is the focus and hot spot of tissue engineering research.[1, 2] The optimum substance for a bone implant should not only have the same elastic modulus and mechanical strength as bone, but also have good histocompatibility and bone integration ability. At present, the most commonly used metal grafts, represented by pure titanium (Ti), titanium alloy or stainless steel, are difficult to adapt to the requirements of bone replacement because of problems including cytotoxicity, low histocompatibility, rapid wear, and high elastic modulus. As a new metal graft material, porous tantalum (Ta) has attracted more and more interest due to its special microstructure, mechanical characteristics and good biocompatibility.[2, 3] In their review article, Han et al.[4] compare the research progress and clinical application of porous Ta and porous Ti fabricated by different methods. As additive manufacturing (AM) technology has advanced in recent years, an increasing number of studies have been carried out on three-dimensional (3D) printing of porous Ta and its gradual application to orthopaedics. The research development and therapeutic application of AM porous Ta in bone tissue engineering are reviewed in this article.

An online search in PubMed, Web of Science, and Elsevier databases dating from 1990 to January 2023 was performed with the key words "additive manufacturing," "3D printed," "tantalum," "bone," and "orthopedics." Two researchers screened all the duplicated literature and checked the cited references independently for veracity. Inclusion criteria were studies reported in English or Chinese language, studies on Ta fabricated using AM technology, and studies related to orthopaedics. Studies were excluded when the Ta used in the studies was not prepared by 3D printing technology or applied to a field unrelated to orthopaedics.

Physical and Chemical Characteristics of Tantalum

Ta (atomic number 73, molecular weight 180.05) is a rare transition metal that is infrequently found in nature. Solid Ta has a density of 16.68 g/cm^3 and a hardness of 6–6.5 Mohs, which is close to diamond. Ta's melting point as a refractory metal is 3017°C. Porous Ta differs from solid metal Ta in its ultra-hardness and density. Porous Ta material has a 3D polyhedral pore structure visible under scanning electron microscopy that is similar to cancellous bone, and the porosity greatly lowers the density of porous Ta material. Ta in its purest form has relatively active chemical characteristics. Ta_2O_5 and TaO_2 are the two major oxide forms in which it is found. The surface of pure Ta spontaneously produces a persistent oxide layer that is non-conductive and resistant to the majority of strong acids and bases when Ta is exposed to air or treated.[5] Consequently Ta is very poorly soluble at all pH levels and potentials. Ta has great corrosion resistance as a result, and it can also lessen the frequency of local inflammation brought on by corrosion products.[6] By altering the surface hydrophobicity and electrostatic effects, the Ta_2O_5 oxide layer on the Ta surface gives good corrosion resistance and also increases cell adhesion. Boyan et al.[7] have demonstrated that hydrophilic surfaces are more favourable to cell adhesion and proliferation. Ta is quite hydrophobic, but as Ta_2O_5 forms, Ta becomes more hydrophilic. On the surface of pure Ta, the static water contact angle is 97.3 ± 4.2°, but it substantially drops to 6.3 ± 1.1° on the surface of Ta_2O_5.[8]

Porous Structure of Tantalum

Bone, including both cancellous bone and cortical bone, has open cells and a 3D interconnected porous structure. High-density orthopaedic implants have a high elastic modulus, which makes them vulnerable to stress shielding, osteolysis, and implant failure. Therefore, porous structures are of interest to researchers. The mechanical properties of 3D-printed Ta scaffolds are influenced by design elements such as porosity, pore size, strut diameter, and pore connectivity.[9]

The mechanical qualities, biocompatibility, and osteogenesis of implants are significantly influenced by the different geometric parameters of the pores in the material.[4, 10] Biemond et al.[11] investigated Ti_6Al_4V implants with wave-like and cuboidal pore designs. The friction coefficient of the wavy porous implant was higher than that of the cubic porous implant, while the bone ingrown depth of the cubic porous implant was much deeper than that of the wavy porous implant. When comparing Ta scaffolds with similar pore characteristics but different pore structures, Markhoff et al.[12] concluded that a pyramidal pore structure is most appropriate for cell migration and proliferation, and they successfully fabricated porous Ta scaffolds with pore geometry of diamond,[13] rhombic dodecahedron,[14] and biomimetic trabeculae.[15]

Cancellous bone has a porosity that ranges from 30% to 95%, and this high porosity provides enough space for cell migration as well as for the transport of nutrients and oxygen.[16, 17] A vast amount of biological research has revealed that implants with higher porosity are more favourable to cell proliferation and bone formation, and also improve biocompatibility, osteogenesis and vascularisation.[12, 17] Wauthle et al.[18] examined the biological characteristics of porous Ta scaffolds generated by selective laser melting (SLM) with a porosity of 80% and determined that high porosity gives good biocompatibility, bone conductivity, and osteogenesis. **Figure 1** presents scanning electron microscopic images of 3D-printed Ta scaffolds with varying porosities.

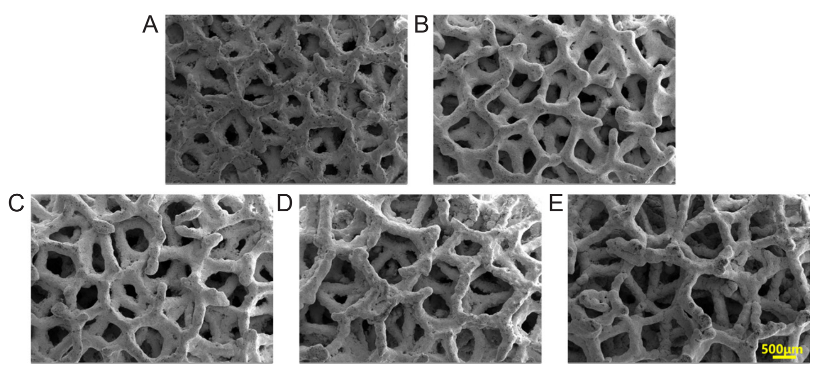

Figure 1. Scanning electron microscopic images of selective laser melting-fabricated porous Ta scaffolds with different porosities. (A–E) 60%, 65%, 70%, 75%, and 80%. Reprinted from Gao et al.[9] Scale bar: 500 μm.

Department of Orthopaedics, Affiliated Zhongshan Hospital of Dalian University, Dalian, Liaoning Province, China

In addition, pore interconnectivity, pore size, and strut diameter are also involved in the mechanical and biological aspects of 3D-printed porous Ta scaffolds. Strut diameter has a significant effect on the mechanical properties of the scaffold, while interpore connectivity plays a significant part in bone conduction, osseointegration, and bone ingrowth.[17] To achieve the desired requirements, the structural parameters of the various pores should be balanced in the Ta scaffold.

Three-Dimensional Printed Porous Tantalum

AM has been identified as a powerful and adaptable processing approach capable of generating porous orthopaedic implants when highly personalised, precise and complicated structures are required. A variety of 3D-printing technologies have been developed in recent years, including SLM, electron beam melting (EBM), direct metal deposition, direct metal printing, fused deposition modelling, direct metal writing, and binder jetting. Among them, SLM and EBM have become the most frequently-utilised technologies for manufacturing porous metal scaffolds because of their benefits of high accuracy, high efficiency, and good stability.

There are similarities in the composition and manufacturing methods of these two technologies. In both systems the point platform rises continually, providing the metal powder, while the blade moves the new Ta powder onto the building platform, where the scaffold is built.

Metal powders are fused together into solid pieces using a laser or electron beam. After the powder layer is established, the frame platform falls, and the next layer of Ta powder that is deposited is hit by the application from the material distribution platform. When the whole construction is complete, the created item is cut free from its base.[10] The difference is that SLM uses a high-energy laser while EBM uses an electron beam. **Figure 2** shows the working mechanism of the SLM and EBM machines.[19, 20]

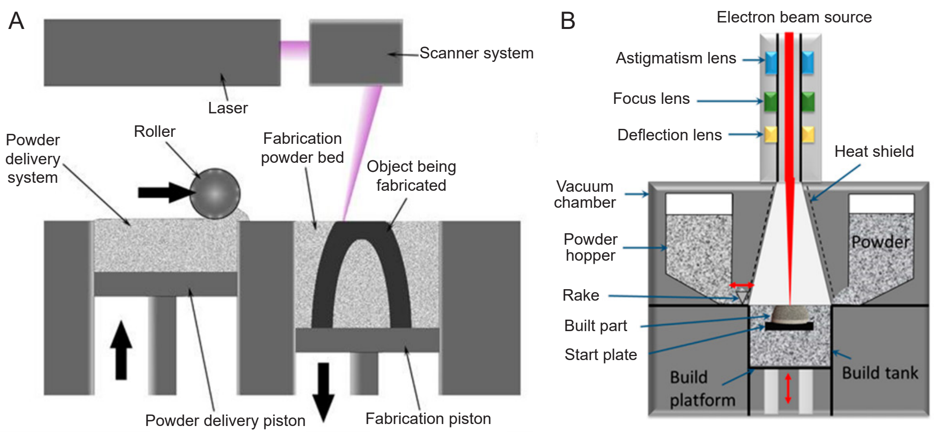

Figure 2. (A) Schematic of the selective laser melting process. Reprinted from Kamran and Farid.[19] (B) An electron beam melting machine. Reprinted from Azam et al.[20]

Compared with chemical vapour deposition and powder metallurgy, the pore formation mechanism of AM is different, resulting in different pore structure characteristics. This allows the AM scaffold to have the finest connectivity and the most adjustable pore characteristics with respect to parameters including strut diameter, pore size, and porosity. Moreover, by designing the geometry according to anatomically-matched requirements, AM can construct highly porous Ta scaffolds. Future porous Ta scaffold preparation will likely rely heavily on AM due to the continuing advances in 3D printing-related technology.

Mechanical Characteristics of Porous Tantalum

Clinical orthopaedic implant materials must have appropriate mechanical characteristics. Especially in the load-bearing area, the maximum strength and relatively low stiffness can enhance the initial biological fusion of the bone around the implant and ensure its long-term stability. In addition, significant indicators for determining the mechanical properties of Ta scaffolds in mechanical analysis include the compressive strength, elastic modulus, tensile strength, fatigue property, and friction coefficient.

The variations in compressive strength of Ta scaffolds are first caused by variations in the pore characteristics, structure, and manufacturing process. The compressive strength of porous Ta prepared using different techniques ranges from 14 to 480 MPa. Therefore, future studies will concentrate on 3D-printed Ta with more advanced compressive strength.[9] Porous Ta has an elastic modulus that is more comparable to that of natural bone than other metallic materials. Because 3D-printed Ta has an elastic modulus closer to that of cancellous bone (0.1–0.5 GPa) and cortical bone (12–18 GPa) than Ti (106–115 GPa), the stress shielding effect is reduced, bone resorption is prevented, and more nearby bone stores are protected.[21] Yang et al.[22] used 3D printing technology to prepare Ta trabecular scaffolds with porosity of 60%, 70% and 80%. In the three-point bending test, the bending strength was approximately 97, 52.8 and 23 MPa, respectively, indicating that as porosity decreased, porous Ta's bending strength increased.[22] More research is required on the flexural strength of 3D-printed Ta scaffolds for extended bone healing, such as ways to enhance the flexural strength by changing the design and structure.

In addition, the fatigue performance of the fabricated porous Ta material also needs to be considered, which can be greatly impacted by different preparation methods. Zardiackas et al.[23] investigated the fatigue behaviour of a porous Ta scaffold prepared by chemical vapour deposition with a porosity of between 75% and 85%. After 5×10^6 cycles of compressive fatigue, the fatigue limit was 23 MPa, and the fatigue limit after 5×10^6 cycles of cantilever bending was 35 MPa.[23] In a compression–compression fatigue test, Wauthle et al.[18] investigated the compressive strength of a 3D-printed Ta scaffold with 80% porosity. They discovered a remarkably low fatigue limit (7.35 MPa at 10^6 cycles). Ta's porous nature and high coefficient of friction can provide additional friction between bone tissue and porous Ta. According to a report,[24] porous Ta has a 40% to 75% higher friction than a conventional porous coating, which is more suited to the stable fixation of an implant and increases surgical success rates.

These excellent mechanical characteristics make porous Ta an effective substitute for human bone tissue. Although the mechanical properties produced by different processing techniques are quite different, this just shows that porous Ta materials have considerable potential in orthopaedic applications, and more in-depth research is needed to identify better manufacturing parameters. For convenience, we have tabulated the mechanical characteristics of AM porous Ta compared with cancellous bone (**Table 1**).[25-28]

Table 1. Mechanical properties of 3D-printed porous Ta

	Manufacturing method	Porosity (%)	Elastic modulus (GPa)	Compressive strength (MPa)	Compressive yield strength (MPa)	Reference
Cancellous bone		50–90	0.01–3.0	–	2–12	25
Ta	SLM	79.7 ± 0.2	1.22 ± 0.07	3.61 ± 0.4	12.7 ± 0.6	15
		38–65	2–20	–	–	18
		68.3 ± 1.1	2.34 ± 0.2	78.54 ± 9.1	–	14
	LENS	27–55	1.5–20	–	–	26
	EBM	75–85	–	–	6.8–24	27
	LMLMC	35.48–50	2.8–9.0	56–480	–	28

Note: '–' indicates no available data. EBM: electron beam melting; LENS: laser near net shaping; LMLMC: laser multi-layer micro-cladding; SLM: selective laser melting; Ta: tantalum.

In Vitro Biological Characteristics of Porous Tantalum

Porous Ta metal has been favoured by researchers in recent years, not only because of its mechanical properties, but more importantly because of its good biocompatibility and good biological characteristics represented by promotion of osteogenesis.

Biocompatibility, cell adhesion, cytotoxicity and proliferation

Porous Ta scaffolds easily combine with oxygen to form a self-passivation surface oxide layer (Ta_2O_5).[29] In addition to preventing corrosion on the scaffold *in vivo*, the surface is extremely stable over a wide pH range. The surface of 3D-printed Ta promotes cell adhesion and proliferation due to its good biological characteristics and durable compatibility with different cell types.[30] With mouse fibroblasts (L929), a 3D-printed Ta scaffold created by Wauthle et al.18 demonstrated good biocompatibility, promoting early integration and bone formation. Wei et al.[31] examined the effectiveness of porous Ta scaffolds in restoring significant cartilage defects in the weight-bearing area. Bone marrow mesenchymal stem cells (BMSCs) and chondrocytes were loaded onto a porous Ta scaffold and subsequently injected into a goat cartilage defect model. The fact that chondrocytes and BMSCs continued to thrive on porous Ta scaffolds 16 weeks after surgery supports the possibility that porous Ta is an important factor in the differentiation of BMSCs into osteoblasts.

The adhesion degree of early cells is crucial for the effective proliferation and differentiation of 3D-printed Ta surfaces.[9] Balla et al.[32] examined the morphological features of osteoblasts cultured on 3D-printed Ta for 3 days through scanning electron microscopy. Osteoblasts were flattened and evenly dispersed across the Ta surface. Comparable results were obtained by Wang et al.[15] and Guo et al.[14] (**Figure 3A**). Dou et al.[33] cultured BMSCs on 3D-printed Ta and porous Ti_6Al_4V, then after 1 day of incubation, they evaluated cell status and number of attachments by fluorescence microscopy in live and dead cells. In comparison to porous Ti_6Al_4V, morphological analysis of stromal stem cells on porous Ta revealed much greater adhesion and extension. Almost every cell on the surface of porous Ta was alive, indicating that porous Ta has good cytocompatibility.

The most frequently-used quantitative assays use 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) or cell counting kit (CCK)-8, which are used to measure cytotoxicity typically through morphological inspection and evaluation of cell viability. Wang et al.[15] investigated whether 3D-printed Ta scaffolds were cytotoxic to mesenchymal stem cells in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium experiment. The optical density values of the Ta and the control group (cells in Dulbecco's modified Eagle medium) showed no significant differences, indicating that porous Ta was not cytotoxic to human mesenchymal stem cells. The proliferation and behaviours of human fibroblasts, osteoblasts, and mesenchymal stem cells were examined by Gee et al.[34] in regard to the effects of porous Ta. They concluded that Ta did not interfere with biological functions in any of these three types of human cells. Other studies on cytotoxicity have also reached similar conclusions.[35, 36]

Dou et al.[33] and Guo et al.[14] used cell counting kit-8 to evaluate the proliferation of BMSCs on the surface of porous Ta and Ti_6Al_4V, and found that porous Ta had a substantially greater ability to promote cell proliferation than porous Ti_6Al_4V (**Figure 3B**).[33] Evaluation using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium measurement assay also reached the same conclusion.[37, 38]

Osteogenesis

Sagomonyants et al.[39] found that porous Ta significantly stimulated the proliferation of human osteoblasts and improved their osteogenic ability compared with other metal materials, and this effect was more prominent in osteoblasts from elderly individuals over 65 years old. Through scanning electron microscopic observation, Wang et al.[40] found that osteoblasts cultured *in vitro* adhered to, proliferated and formed various intercellular connections on the pore surfaces of porous Ta. According to studies,[39, 41] Ta increases the expression of genes associated with osteoblasts and certain cytokines while decreasing the expression of genes connected with osteoclasts. This encourages the proliferation, differentiation and mineralisation of osteoblasts. The findings demonstrated that the expressions of bone morphogenetic protein-2, alkaline phosphatase, osteocalcin, and osteopontin were noticeably greater in the experimental group than in the control group.[42] The differentiation potential of human foetal osteoblasts cultured on porous Ta and porous Ti scaffolds is similarly influenced by the expression of the alkaline phosphatase protein. Confocal images (**Figure 3C**) showed that porous Ta scaffolds had a higher expression of vinculin protein than porous Ti scaffolds.[32] Temponi et al.[38] assessed the biological behaviour of human peripheral blood mononuclear cells interacting with porous Ta. Porous Ta did not change the activity of peripheral blood mononuclear cells compared to the control group, while also allowing cell adhesion, reducing receptor activator of nuclear factor-kappa B ligand (RANKL) expression, and enhancing transforming growth factor-β expression.[43] In addition, the surface characteristics of implanted Ta can be modified using a variety of techniques, including sandblasting, alkali heat treatment, anodic oxidation, coating and surface functionalisation. These surface treatment technologies can enhance the osteogenic properties of the material.[44-47]

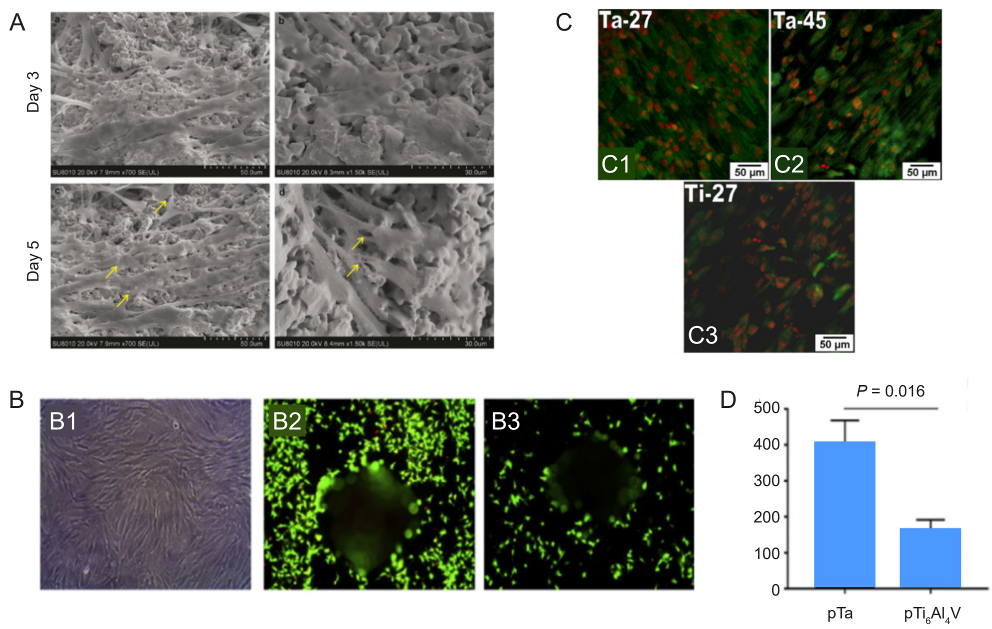

Figure 3. Cell adhesion and proliferation properties on porous Ta. (A) Morphology of mesenchymal stem cells (yellow arrows) cultured for 3 and 5 days. Reprinted from Wang et al.[15] (B) Light (B1) and fluorescence microscopic images of live-dead-stained bone marrow mesenchymal stem cells incubated on porous Ta (B2) and Ti_6Al_4V (B3) for 1 day, and quantification of the adherent cells (B4). Reprinted from Dox et al.[33](C) Confocal micrographs of vinculin expression on porous Ta with porosities of 27% (C1) and 45% (C2) and on porous Ti with 27% porosity (C3). Reprinted from Balla et al.[32] Copyright © 2010 Acta Materialia Inc. Scale bars: 50 μm. Ta: tantalum; Ti: titanium.

Angiogenesis

Oxygen and nutrients required for osteogenesis are delivered by newly-formed blood vessels, and the role of angiogenesis is to promote the continuing stability of bone implant materials.[47] Porous Ta, polydopamine–porous Ta scaffolds, polydopamine–magnesium ion porous Ta scaffolds, and polydopamine–strontium ion porous Ta scaffolds were all thoroughly investigated by Cheng et al.[49] for their impact on the ability of human umbilical vein endothelial cells to form and migrate *in vitro*. Their findings confirmed that the porous Ta scaffold was beneficial to angiogenesis. *In vitro*, the vascularisation rate of porous Ta scaffold materials can be enhanced by the addition of Sr and Mg ions.

Antibacterial activity

Whether or not porous Ta has antibacterial properties is still controversial. Studies conducted by Zhang and colleagues[50, 51] revealed that a TaN coating exhibited excellent anti-bacterial properties against various types of bacteria, such as Staphylococcus aureus and Porphyromonas gingivalis. In another study, the use of Ta-based components in 966 patients who had undergone total hip arthroplasty significantly decreased the likelihood of infection.[52] Compared to Ti, the infection rate of Ta was lower at 3.1%. This suggests that it confers some resistance against infection.

The porous nature of Ta materials and their rough surfaces are helpful for tissue growth and early implant durability, but they also create favourable circumstances for bacterial colonisation.[53] In *in vivo* environments, porous Ta prostheses demonstrated adequate osseointegration ability even when the implanted site was in a long-term infected state, but 3D-printed Ta failed to demonstrate intrinsic anti-biofilm qualities *in vitro*.[54, 55] According to a study by Yang et al.,[56] this could be the outcome of the host immunological reaction brought on by porous Ta. Other research has yielded inconclusive results regarding the capacity of porous Ta to fend off infection *in vivo*.[57] There is still much disagreement in academia as to whether Ta has intrinsic antibacterial properties.

Preclinical Experiments using Tantalum

Many scholars have verified the osseointegration and osteogenic characteristics of porous Ta scaffolds *in vivo* through animal experiments. As mentioned above, porous Ta implants with open, interconnected structures are beneficial for osteoblast adhesion and proliferation as well as the passage of nutrients and oxygen needed for the formation of new bone. The oxygen concentration and acidic conditions of porous Ta scaffold were verified by Jonitz et al.[47] to be advantageous for bone ingrowth. At 16 weeks after surgery, Wang et al.[58] completed 3D reconstruction of micro-computed tomography scans and estimated the quantity percentage of bone formed around porous Ta implants in rabbits with condylar osteochondral defects. They indicated that the interior of the porous Ta implant as well as its surface had been penetrated by freshly-formed bone. The right hind legs of rabbits were surgically implanted with porous 3D-printed Ta and Ti_6Al_4V implants by Guo et al.[14] Radiographs taken at 4, 8, and 12 weeks, shown in **Figure 4A**, revealed that porous Ta specimens integrated into the surrounding bone tissue more successfully than porous Ti_6Al_4V specimens and prevented loosening or dislocation.[14] Wauthle et al.[18] conducted histological evaluation of a porous Ta implant removed from a rat femoral defect and found that the pores of the implant supported strong new bone growth, and the porous Ta scaffold was successfully incorporated into the surrounding tissue (**Figure 4B**). In conclusion, the superior osseointegration and osteoconductivity of porous Ta facilitated bone tissue remodelling and regeneration.

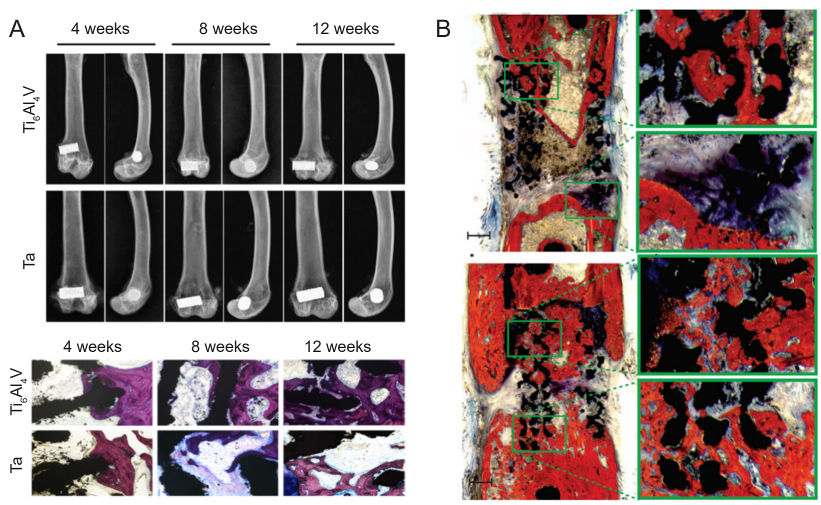

Figure 4. Osseointegration of porous tantalum (Ta) scaffolds. (A) Radiographic and histological images of porous Ta and Ti_6Al_4V implants at 4, 8, and 12 weeks. Reprinted from Guo et al.[14] (B) Histological images of SLM porous Ta after 12 weeks *in vivo*. Reprinted from Wauthle et al.[18] Copyright © 2014 Acta Materialia Inc.

The term "osseointegration" refers to the process in which an implant is enveloped by surrounding bone tissue or comes into contact directly with it. Porous Ta scaffolds have solid osseointegration after implantation, good *in vitro* biocompatibility, and no early, evident allergic reactions.[59] In the right hind leg of rabbits, Guo et al.[14] implanted porous Ta and Ti_6Al_4V implants. Radiographs taken at 4, 8, and 12 weeks revealed that the porous Ta samples prevented loosening or dislocation more successfully than the porous Ti_6Al_4V samples. Wang et al.[60] used micro-computed tomography analysis to evaluate the volume of new bone around porous Ta implants and compared them with porous Ti implants at 6 and 12 weeks. They discovered that the volume of new bone around the porous Ta implants was much greater than that surrounding the porous Ti implants.[60] Porous Ta rods were inserted into the hind legs of dogs by Wei et al.[61] and evaluated by a hard tissue biopsy 3 to 6 weeks after implantation. They found that new osteoblast adhesion and new bone ingrowth were seen at the Ta-host bone contact area and the pores. Three and six months after implantation, the Ta rod from a canine femoral shaft defect model was analysed by Van Gieson staining by Wang et al.[15] The study revealed that the bonding strength between the 3D-printed Ta and the host bone was significantly greater after 6 months, and examination of hard tissue sections demonstrated that the new bone was firmly bonded to the surface of the Ta implant. In a rabbit tibial repair model, Fraser et al. implanted Ti implants at the neck and root tip together with a mid-connected implant constructed of porous Ta.[62] They observed that new bone growth occurred more frequently around the middle of the implant than at the neck and tip of the root because of the greater interaction with the surrounding soft and hard tissues.

The potential of porous Ta in bone functional regeneration is demonstrated by the abundance of blood vessels that emerge at the interface and inside the prosthesis as new bone tissue grows into the implant. After 4, 8, and 16 weeks of healing, Hacking et al.[63] removed subcutaneous porous Ta implants from the backs of dogs and used transmission light microscopy to examine their histological sections. The porous Ta stent was discovered to include a significant proportion of vascularised connective fibrous tissue 16 weeks after placement. After removing porous Ta implants from dog femurs 52 weeks after they were implanted, Bobyn et al.[64] discovered identical histological evidence of vascular supply throughout the endophytic bone. These results confirmed that porous Ta promotes vasculogenesis, but the angiogenic mechanisms and factors affecting angiogenesis in porous Ta scaffolds have not been clarified.

Drug Delivery of Porous Tantalum

In the past few years, the use of porous structures to deliver drugs has become a research hotspot. Porous Ta metal has become one of the best choices for drug-loaded scaffolds due to its good biocompatibility. Surface modification by dip coating, hydrogel packaging, and spray coating are examples of drug-loading techniques. Multiple studies have shown that porous Ta metal itself has no observable antibacterial effect *in vitro*.[53, 65] However, porous Ta promotes innate immunity and antibacterial actions *in vivo*.[55] Carrying antibiotics to fight infection has become the main use of drug delivery. Functional reconstruction and adjuvant therapy after tumour resection are another use of porous Ta metallic materials for drug delivery. Guo et al.[66] used hydrogel and electrostatic interaction techniques to load doxorubicin onto 3D-printed porous Ta and showed that this technique successfully extended the duration of medication release. Some scholars further enhanced the osteogenic effect of Ta metal by drug loading. For repairing bone defects, Tanzer et al.[67] used 3D-printed porous Ta and surgically implanted a porous Ta stent carrying zoledronic acid into the proximal femurs of dogs. Compared to a blank control group, the bone mass around the prosthesis was 2.34 times greater in the experimental group than the control group, and bone growth was 58% higher. In addition, other studies using implants loaded with vascular endothelial growth factor or transforming growth factor have verified the increased repair ability after drug loading.[68, 69] High local drug concentration, long release duration, and low toxicity are all benefits of the porous Ta metal drug delivery system; however clinical transformation application and drug dosage optimization still need to be improved.[70] **Figure 5** shows different methods of loading cells or medications onto porous Ta.

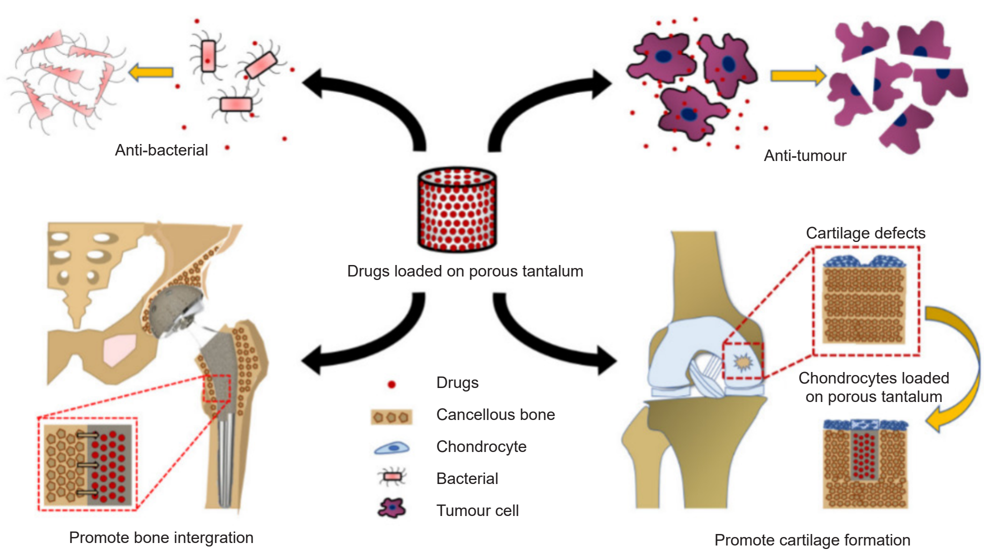

Figure 5. Drugs or cells loaded onto porous tantalum (Ta) for different treatments. Copyright 2021 from Hua et al.[70] Reproduced by permission of Taylor and Francis Group, LLC, a division of Informapic.

Clinical Translation of Porous Tantalum

As mentioned above, porous Ta has excellent biological properties, an elastic modulus comparable to human cancellous bone, sufficient mechanical strength, and excellent corrosion resistance. Since Kaplan et al.[71] first developed Ta implants with an open cell structure in 1994, porous Ta metal implants are being used more frequently in orthopaedic procedures such as foot and ankle surgery, shoulder reconstruction, spinal fusion, and hip and knee replacement. The effectiveness and safety of 3D-printed Ta implants have been the subject of an increasing number of clinical trials. **Figure 6** shows several instances of 3D-printed porous Ta implants applied in orthopaedic surgery.[72, 73]

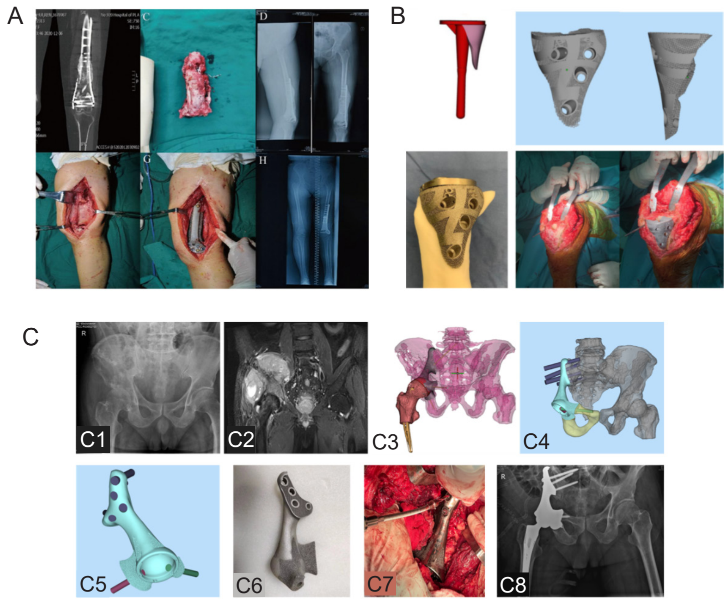

Figure 6. Clinical translation of 3D-printed porous Ta. (A) The clinical application of customized 3D-printed porous Ta scaffolds combined with Masquelet's induced membrane technique to reconstruct an infected segmental femoral defect. Reprinted from Wu et al.[72] (B) Knee reconstruction using 3D-printed porous Ta augmentation in the treatment of a Charcot joint. Reprinted from Hua et al.[73] (C) After pelvic tumour resection, hemi-pelvic replacement surgery was performed using 3D-printed porous Ta implants. (C1) Anteroposterior X-ray of the patient's hip joint showed an uneven density of the right iliac crest. (C2) Coronal MRI showed the extent of tumour invasion. (C3) Preoperative simulation of tumour resection and reconstruction range and location. (C4) Hemi-pelvic prosthesis design to restore the pelvic ring structure. (C5) Lateral view of the hemi-pelvic prosthesis. (C6) 3D-printed hemi-pelvic prosthesis. (C7) Intraoperative prosthesis implantation. (C8) X-ray at 6 months after surgery. C was from the authors' original study. 3D: three-dimensional; MRI: magnetic resonance imaging; Ta: tantalum.

Hip

At present, porous Ta implants are frequently used in three types of hip surgery: developmental dysplasia of the hip acetabular shelf, femoral head necrosis support, and hip reconstruction. Cheng et al.[74] reported a study on the application of individualised porous Ta metal acetabular shelf augments prepared by 3D-printing technology for hip joint reconstruction in the treatment of adult developmental dysplasia of the hip. Eight patients with Crowe type I developmental dysplasia of the hip were included in this study. Individual 3D-modelling of the hip joint was performed by computer. The most appropriate size of the acetabular shelf was designed using specialised software MIMICS (Materialise, Leuven, Belgium), and then the porous acetabular augment was processed. The visual analogue scale score decreased from 2.92 ± 0.79 preoperatively to 0.83 ± 0.72 at the last follow-up, and the Harris hip score increased from 69.67 ± 4.62 preoperatively to 84.25 ± 4.14 at the final follow-up. Imaging analysis revealed that the Ta metal acetabular augment was in tight contact with the iliac bone and exhibited no loosening or osteoarthritis progression, and the changes were statistically significant.

In the treatment of osteonecrosis of the femoral head (ONFH), a porous Ta rod plays the role of filling and supporting a femoral head with a bone defect after core decompression, and stimulating osteogenesis of the host bone in the subchondral bone area. Studies have shown that a porous Ta rod can slow the progress of early osteonecrosis and delay the time of joint replacement.[75, 76] Liu et al.[77] reported that 149 patients with early ONFH were treated with porous Ta rods, and the follow-up study after 3 years showed good clinical and imaging results. However, the long-term effect of Ta rods is controversial.[78] One study showed that the mechanical support of the necrotic area by porous Ta rods is insufficient, and only 1.9% of the bone ingraft was observed in histopathological examination of the 15 Ta rods removed.[79] Therefore, some scholars have tried to combine vascularised bone flap transplantation or BMSCs with porous Ta rods.[80, 81] To confirm the efficacy of these techniques, long-term clinical follow-up surveillance is still required to evaluate these improvements.

The use of porous Ta material in total hip arthroplasty is mainly in the acetabular cup. In 2002, experts directly pressed polyethylene lining into a porous Ta cup, and this integrated design reduced wear of the polyethylene.[82] Wear debris has been considered as the main cause of aseptic loosening of the acetabular cup, so this design can theoretically prolong the service life of the artificial joint. In a clinically available prospective study, 151 hips were followed up for 8–10 years after primary total hip arthroplasty.[83] Although periacetabular spaces of 1 to 5 mm in length could be identified early in 25 hips, these disappeared after 24 weeks. No complications such as osteolysis or prosthesis loosening were confirmed by follow-up radiographs. On the surface of the porous Ta cup, there was significant bone ingrowth in a patient who underwent revision surgery due to dislocation 50 months after surgery. Eighty-two patients who underwent total hip replacement with a porous Ta acetabular component were observed by Macheras et al.[84] for an average of 7.3 years. At 6 months following surgery, the gap between the prosthesis and the surrounding bone was filled with new bone tissue, and at the latest follow-up, there were no radiolucent lines or indications of periprosthetic osteolysis.[84] For revision total hip arthroplasty, bone defect repair and acetabulum reconstruction, as well as restoration of basic stability, centre of rotation, and maximum bone–implant contact, are surgical challenges.[85] Several short-term and medium-term studies have shown that porous Ta acetabular cups and patches provide good results in the treatment of acetabular bone defects.[86, 87] Löchel et al.[88] performed a 10-year follow-up after hip revision surgery using a porous Ta cup and augment. The survival rate of 53 hips with complete follow-up was 92.5%. The Harris hip score increased significantly after revision surgery.

Knee

Porous Ta materials are also frequently used in knee reconstruction surgery. In short-term and long-term postoperative follow-up studies, the replacement of a conventional prosthesis with a cementless porous Ta single-piece tibial prosthesis achieved good clinical results.[89-91] De Martino et al.[92] described results in 33 patients who underwent primary total knee arthroplasty (TKA) with a cementless Ta single tibial component in a study with postoperative follow-up of at least 10 years. None of the prostheses were subjected to radiological examination for osteolysis, or displacement. The individuals' average knee scores increased from 56 before surgery to 93 afterward, showing that porous Ta is a promising alternative material for TKA prosthesis. The construction of this tibial monolithic component is comparable to that of the acetabular monolithic replacement in that polyethylene is directly compressed into the porous Ta substrate, eliminating the possibility of wear debris penetrating the bone–implant interface. The mechanical and biological characteristics of the porous Ta ensure the primary stability and long-term survival of the tibial component. Significant bone ingrowth was found in the column and posterior floor plate interface of a porous Ta tibial prosthesis that was recovered from a chronically-infected knee prosthesis through histological analysis, indicating that even in an infected environment, good bone-implant fusion can still be achieved.[93]

The treatment of bone defects in the distal femur, proximal tibia and even patella in knee reconstruction has always been one of the difficulties in surgery. Porous Ta grafts are used for structural transplantation and various irregular shapes can be designed and prepared to restore the required bone reserve depending on location and the amount of bone lost.[94] A number of medium-term follow-up studies have shown that porous Ta vertebrae have a good effect on restoring huge bone defects and maintaining the stability of prostheses, whether in the femoral or tibial sides.[95, 96] Another systematic review of Ta cones and cannulas revealed a 9.7% reoperation rate and a 0.8% sterile loosening rate per cannula. The reoperation rate of Ta vertebrae was 18.7%, and the aseptic loosening rate was 1.7%.[97] Patellar reconstruction with a porous Ta prosthesis is a way to restore the normal structure and function of the patellofemoral joint in cases of knee extension device dysfunction due to patellar resection or patellar bone defect. In a clinical study, Kamath et al.[98] investigated the use of a porous Ta patellar component to treat severe patellar loss during revision TKA. All 23 participants had positive clinical outcomes at the most recent follow-up (mean 7.7 years), as measured by the Oxford Knee Score and the Knee Society Score.[98]

Spine

Porous Ta scaffolds are commonly used in lumbar interbody fusion and cervical interbody fusion in spinal repair applications.[99] A porous Ta cage used in anterior cervical fusion was proven to be beneficial in a prospective randomized controlled clinical experiment by Fernández-Fairen et al.[100] The Ta cage implantation group revealed a similar fusion rate and postoperative stability at the conclusion of a 2-year follow-up period compared to the standard autogenous iliac bone transplant paired with an anterior wall plate. Patients who received single-hole Ta cage implantation for interbody fusion had good clinical and radiological outcomes after 11 years of follow-up, with no significant complications in 12 patients. In addition, Mastronardi et al.[101] showed that porous Ta was beneficial in terms of interbody fusion rate, low complication rate, and short- or long-term postoperative evaluation scores, such as 36-item short-form, neck disability index, and visual analogue scale. Lebhar et al.[102] also revealed the preliminary stability and osseointegration of Ta interbody implants in the medium-term follow-up of posterior lumbar interbody fusion, and the results confirmed that porous Ta implants are a reliable choice for spinal fusion surgery. Surgical time, blood loss, length of hospital stay, fusion rate, and visual analogue scale scores, and complication rates from pertinent clinical studies, were all examined in two recent meta-analyses. We discovered through two meta-analyses that porous Ta implants, which have been the gold standard in the surgical treatment of anterior cervical degenerative disc degeneration, are equally effective and safe.[37, 103]

Foot and ankle

End-stage ankle arthritis is a very serious disease. In the case of ineffective conservative treatment, ankle arthrodesis and ankle replacement are two commonly-used surgical treatments.[104] Horisberger et al.[105] revealed the use of a Ta spacer to reconstruct major ankle bone defects during ankle arthrodesis. Postoperative X-rays confirmed that the structure had good initial stability.[105] Five years after surgery, Tiusanen et al.[106] reported 104 patients who had undergone total ankle replacement with a porous Ta prosthesis. Low rates of osteolysis and prosthesis loosening were found, and patient pain and functional outcomes were encouraging, indicating that Ta is an effective substitute for traditional bone grafting in foot and ankle applications.[106] Sundet et al.[107] used a combination of retrograde screws, a porous Ta spacer, and an osteoinductive augment with autologous bone marrow concentrate during revision surgery on 30 patients (31 ankles) who had undergone a failed total ankle replacement. The fusion rate was 93.5% after a mean follow-up of 23 months, and almost all patients were satisfied with the procedure, with pain relief and improved mobility. Although the survival rate of TKA has been shown to be lower than that of hip and knee replacement, some studies have recommended retaining the range of motion and normal gait of the ankle rather than using arthrodesis.[99, 108] The tibial and talar components of a porous Ta-based ankle prosthesis taken out of a 50-year-old female patient had a higher percentage of bone ingrowth than the porous Ta hip and knee components that were retrieved. At the same time, active bone remodelling was still visible in the porous Ta layer 3 years after operation.[109]

Others

In a case reported by Zhao et al.,[110] a 3D-printed porous Ta plate was used to treat tibial fracture nonunion, and the patient was able to perform normal activities 10 weeks after surgery without pain in the affected limb. The fracture had fully healed at the 5-month follow-up, and the patient was able to return to work and normal activities.[110] In order to manage challenging proximal humeral fractures, Li et al.[111] observed 51 patients who had undergone total shoulder arthroplasty utilizing a porous Ta prosthesis. After an average follow-up period of 3 years, radiographic evaluation showed anatomical union of the greater tuberosity of the shoulder in 92% of enrolled patients, and there was no evidence of an infection or of prosthesis loosening. Using monoblock porous Ta glenoid components, Chen et al. revealed good clinical results in patients with no loosening of the glenoid component or need for revision surgery regardless of preoperative glenoid morphology.[112] Sasanuma et al.[113] also demonstrated that in elderly patients with chronic comminuted proximal humeral fractures, the reverse shoulder arthroplasty group using porous Ta implants had a higher rate of bone healing and a greater range of shoulder motion than the group using nonporous stents.

Summary

Recently, porous Ta metal has attracted more attention as a new orthopaedic implant material. With the deepening of research and the progress of technology, the advantages of porous Ta metal materials in mechanics and biology have been gradually highlighted. The use of Ta is not limited to orthopaedic equipment such as porous Ta rods and intervertebral fusion cages, but it has also been applied to complex implants such as artificial hip and knee prostheses. Three-dimensional printing technology has the advantages of sufficient design freedom and personalised customisation when dealing with the complex morphology of human body structure. It is easier to load different medications onto the porous surface of the material, but it is challenging to maintain the biological activity and regulate the kinetics of its delayed release. However, its clinical application still faces problems such as high cost, a complex preparation process, and inadequately slow osseointegration. *In vivo* safety also needs to be supported by more research evidence. In addition, the mechanism of action involved in the biological effects of Ta metals requires more comprehensive and in-depth exploration, including the development of proteomics and genomics. It is necessary for researchers from materials science, biology, medicine and other disciplines to cooperate. Future studies will focus on porous Ta metal materials with easy preparation processes, low costs, and superior performance.

There are some limitations in this review. Publication bias was assessed but could not be ruled out. In addition not all clinically-pertinent topics can be addressed by this analysis, and some of the results may be challenging to put into practice. However, the authors provided an innovative viewpoint on how to introduce Ta into bone repair materials using advances in AM technology. We hope that this review will provide a succinct explanation of the potential of Ta as a bone implant material in the near future.

Author contributions

Conceptualization: DZ, JY; definition of intellectual content: LC, JL; literature search: HY, PY, HW, LL; manuscript preparation and editing: JY, HY, LS, BW; manuscript review: DZ. All authors approved the final version of the manuscript.

Financial support

This work was supported by the General Program of the National Natural Science Foundation of China, No. 82172398.

Acknowledgement

None.

Conflicts of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Li, J. J.; Ebied, M.; Xu, J.; Zreiqat, H. Current approaches to bone tissue engineering: the interface between biology and engineering. *Adv Healthc Mater.* **2018**, *7*, e1701061.
2. Ghassemi, T.; Shahroodi, A.; Ebrahimzadeh, M. H.; Mousavian, A.; Movaffagh, J.; Moradi, A. Current concepts in scaffolding for bone tissue engineering. *Arch Bone Jt Surg.* **2018**, **6**, 90-99.
3. Asri, R. I. M.; Harun, W. S. W.; Samykano, M.; Lah, N. A. C.; Ghani, S. A. C.; Tarlochan, F.; Raza, M. R. Corrosion and surface modification on biocompatible metals: A review. *Mater Sci Eng C Mater Biol Appl.* **2017**, *77*, 1261-1274.

4. Han, Q.; Wang, C.; Chen, H.; Zhao, X.; Wang, J. Porous tantalum and titanium in orthopedics: a review. *ACS Biomater Sci Eng*. **2019**, *5*, 5798-5824.
5. Cardonne, S. M.; Kumar, P.; Michaluk, C. A.; Schwartz, H. D. Tantalum and its alloys. *Int J Refract Met Hard Mater*. **1995**, *13*, 187-194.
6. Zhang, L.; Haddouti, E. M.; Beckert, H.; Biehl, R.; Pariyar, S.; Rüwald, J. M.; Li, X.; Jaenisch, M.; Burger, C.; Wirtz, D. C.; Kabir, K.; Schildberg, F. A. Investigation of cytotoxicity, oxidative stress, and inflammatory responses of tantalum nanoparticles in THP-1-derived macrophages. *Mediators Inflamm*. **2020**, *2020*, 3824593.
7. Boyan, B. D.; Lotz, E. M.; Schwartz, Z. * Roughness and hydrophilicity as osteogenic biomimetic surface properties. *Tissue Eng Part A*. **2017**, *23*, 1479-1489.
8. Chang, Y. Y.; Huang, H. L.; Chen, H. J.; Lai, C. H.; Wen, C. Y. Antibacterial properties and cytocompatibility of tantalum oxide coatings. *Surf Coat Technol*. **2014**, *259*, 193-198.
9. Gao, H.; Yang, J.; Jin, X.; Qu, X.; Zhang, F.; Zhang, D.; Chen, H.; Wei, H.; Zhang, S.; Jia, W.; Yue, B.; Li, X. Porous tantalum scaffolds: FABRICATION, structure, properties, and orthopedic applications. *Mater Des*. **2021**, *210*, 110095.
10. Wang, Z.; Wang, C.; Li, C.; Qin, Y.; Zhong, L.; Chen, B.; Li, Z.; Liu, H.; Chang, F.; Wang, J. Analysis of factors influencing bone ingrowth into three-dimensional printed porous metal scaffolds: a review. *J Alloys Compd*. **2017**, *717*, 271-285.
11. Biemond, J. E.; Aquarius, R.; Verdonschot, N.; Buma, P. Frictional and bone ingrowth properties of engineered surface topographies produced by electron beam technology. *Arch Orthop Trauma Surg*. **2011**, *131*, 711-718.
12. Markhoff, J.; Wieding, J.; Weissmann, V.; Pasold, J.; Jonitz-Heincke, A.; Bader, R. Influence of different three-dimensional open porous titanium scaffold designs on human osteoblasts behavior in static and dynamic cell investigations. *Materials (Basel)*. **2015**, *8*, 5490-5507.
13. Wang, H.; Su, K.; Su, L.; Liang, P.; Ji, P.; Wang, C. Comparison of 3D-printed porous tantalum and titanium scaffolds on osteointegration and osteogenesis. *Mater Sci Eng C Mater Biol Appl*. **2019**, *104*, 109908.
14. Guo, Y.; Xie, K.; Jiang, W.; Wang, L.; Li, G.; Zhao, S.; Wu, W.; Hao, Y. In vitro and in vivo study of 3D-printed porous tantalum scaffolds for repairing bone defects. *ACS Biomater Sci Eng*. 2019, *5*, 1123-1133.
15. Wang, X.; Zhu, Z.; Xiao, H.; Luo, C.; Luo, X.; Lv, F.; Liao, J.; Huang, W. Three-dimensional, multiscale, and interconnected trabecular bone mimic porous tantalum scaffold for bone tissue engineering. *ACS Omega*. **2020**, *5*, 22520-22528.
16. Keaveny, T. M.; Morgan, E. F.; Niebur, G. L.; Yeh, O. C. Biomechanics of trabecular bone. *Annu Rev Biomed Eng*. **2001**, *3*, 307-333.
17. Karageorgiou, V.; Kaplan, D. Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials*. **2005**, *26*, 5474-5491.
18. Wauthle, R.; van der Stok, J.; Amin Yavari, S.; Van Humbeeck, J.; Kruth, J. P.; Zadpoor, A. A.; Weinans, H.; Mulier, M.; Schrooten, J. Additively manufactured porous tantalum implants. *Acta Biomater*. **2015**, *14*, 217-225.
19. Kamran, S.; Farid, A. Microstructure-tailored stainless steels with high mechanical performance at elevated temperature. In *Stainless Steels and Alloys*, Zoia, D., ed. IntechOpen: Rijeka, **2018**; p Ch. 7.
20. Azam, F. I.; Abdul Rani, A. M.; Altaf, K.; Rao, T. V. V. L. N.; Zaharin, H. A. An in-depth review on direct additive manufacturing of metals. *IOP Conf Ser Mater Sci Eng*. **2018**, *328*, 012005.
21. Liu, Y.; Bao, C.; Wismeijer, D.; Wu, G. The physicochemical/biological properties of porous tantalum and the potential surface modification techniques to improve its clinical application in dental implantology. *Mater Sci Eng C Mater Biol Appl*. **2015**, *49*, 323-329.
22. Yang, J.; Jin, X.; Gao, H.; Zhang, D.; Chen, H.; Zhang, S.; Li, X. Additive manufacturing of trabecular tantalum scaffolds by laser powder bed fusion: Mechanical property evaluation and porous structure characterization. *Mater Charact*. **2020**, *170*, 110694.
23. Zardiackas, L. D.; Parsell, D. E.; Dillon, L. D.; Mitchell, D. W.; Nunnery, L. A.; Poggie, R. Structure, metallurgy, and mechanical properties of a porous tantalum foam. *J Biomed Mater Res*. **2001**, *58*, 180-187.
24. Stiehl, J. B. Trabecular metal in hip reconstructive surgery. *Orthopedics*. **2005**, *28*, 662-670.
25. Yang, M.; Ma, H.; Shen, Z.; Huang, Z.; Tian, Q.; Tian, J. Dissimilar material welding of tantalum foil and Q235 steel plate using improved explosive welding technique. *Mater Des*. **2020**, *186*, 108348.
26. Qian, H.; Lei, T.; Lei, P.; Hu, Y. Additively manufactured tantalum implants for repairing bone defects: a systematic review. *Tissue Eng Part B Rev*. **2021**, *27*, 166-180.
27. Tang, H. P.; Yang, K.; Jia, L.; He, W. W.; Yang, L.; Zhang, X. Z. Tantalum bone implants printed by selective electron beam manufacturing (SEBM) and their clinical applications. *JOM*. **2020**, *72*, 1016-1021.
28. Chen, C.; Li, Y.; Zhang, M.; Wang, X.; Zhang, C.; Jing, H. Effect of laser processing parameters on mechanical properties of porous tantalum fabricated by laser multi-layer micro-cladding. *Rapid Prototyp J*. **2017**, *23*, 758-770.
29. Maccauro, G.; Iommetti, P. R.; Muratori, F.; Raffaelli, L.; Manicone, P. F.; Fabbriciani, C. An overview about biomedical applications of micron and nano size tantalum. *Recent Pat Biotechnol*. **2009**, *3*, 157-165.
30. Cheng, X.; Wan, Q.; Pei, X. Graphene family materials in bone tissue regeneration: perspectives and challenges. *Nanoscale Res Lett*. **2018**, *13*, 289.
31. Wei, X.; Zuo, X.; Yang, B. In Sequential recommendation based on long-term and short-term user behavior with self-attention, Knowledge Science, Engineering and Management, Cham, 2019// Douligeris, C.; Karagiannis, D.; Apostolou, D., eds. Springer International Publishing: Cham, **2019**; pp 72-83.
32. Balla, V. K.; Bodhak, S.; Bose, S.; Bandyopadhyay, A. Porous tantalum structures for bone implants: fabrication, mechanical and in vitro biological properties. *Acta Biomater*. **2010**, *6*, 3349-3359.
33. Dou, X.; Wei, X.; Liu, G.; Wang, S.; Lv, Y.; Li, J.; Ma, Z.; Zheng, G.; Wang, Y.; Hu, M.; Yu, W.; Zhao, D. Effect of porous tantalum on promoting the osteogenic differentiation of bone marrow mesenchymal stem cells in vitro through the MAPK/ERK signal pathway. *J Orthop Translat*. **2019**, *19*, 81-93.
34. Gee, E. C. A.; Eleotério, R.; Bowker, L. M.; Saithna, A.; Hunt, J. A. The influence of tantalum on human cell lineages important for healing in soft-tissue reattachment surgery: an in-vitro analysis. *J Exp Orthop*. **2019**, *6*, 40.
35. Lu, M.; Xu, S.; Lei, Z. X.; Lu, D.; Cao, W.; Huttula, M.; Hou, C. H.; Du, S. H.; Chen, W.; Dai, S. W.; Li, H. M.; Jin, D. D. Application of a novel porous tantalum implant in rabbit anterior lumbar spine fusion model: in vitro and in vivo experiments. *Chin Med J (Engl)*. **2019**, *132*, 51-62.
36. Wei, X.; Liu, B.; Liu, G.; Yang, F.; Cao, F.; Dou, X.; Yu, W.; Wang, B.; Zheng, G.; Cheng, L.; Ma, Z.; Zhang, Y.; Yang, J.; Wang, Z.; Li, J.; Cui, D.; Wang, W.; Xie, H.; Li, L.; Zhang, F.; Lineaweaver, W. C.; Zhao, D. Mesenchymal stem cell-loaded porous tantalum integrated with biomimetic 3D collagen-based scaffold to repair large osteochondral

defects in goats. *Stem Cell Res Ther.* **2019**, *10*, 72.
37. Wang, Y.; Wei, R.; Subedi, D.; Jiang, H.; Yan, J.; Li, J. Tantalum fusion device in anterior cervical discectomy and fusion for treatment of cervical degeneration disease: a systematic review and meta-analysis. *Clin Spine Surg.* **2020**, *33*, 111-119.
38. Temponi, E. F.; Souza, P. E. A.; Souto, G. R.; Magalhães, L. M. D.; Dutra, W. O.; Gollob, K. J.; Silva, T. A.; Soares, R. V. Effect of porous tantalum on the biological response of human peripheral mononuclear cells exposed to Porphyromonas gingivalis. *J Investig Clin Dent.* **2019**, *10*, e12472.
39. Sagomonyants, K. B.; Hakim-Zargar, M.; Jhaveri, A.; Aronow, M. S.; Gronowicz, G. Porous tantalum stimulates the proliferation and osteogenesis of osteoblasts from elderly female patients. *J Orthop Res.* **2011**, *29*, 609-616.
40. Wang, Q.; Zhang, H.; Li, Q.; Ye, L.; Gan, H.; Liu, Y.; Wang, H.; Wang, Z. Biocompatibility and osteogenic properties of porous tantalum. *Exp Ther Med.* **2015**, *9*, 780-786.
41. Jonitz, A.; Lochner, K.; Lindner, T.; Hansmann, D.; Marrot, A.; Bader, R. Oxygen consumption, acidification and migration capacity of human primary osteoblasts within a three-dimensional tantalum scaffold. *J Mater Sci Mater Med.* **2011**, *22*, 2089-2095.
42. Wang, F.; Li, C.; Zhang, S.; Liu, H. Tantalum coated on titanium dioxide nanotubes by plasma spraying enhances cytocompatibility for dental implants. *Surf Coat Technol.* **2020**, *382*, 125161.
43. Qian, H.; Lei, T.; Ye, Z.; Hu, Y.; Lei, P. From the performance to the essence: the biological mechanisms of how tantalum contributes to osteogenesis. *Biomed Res Int.* **2020**, *2020*, 5162524.
44. Wang, X.; Ning, B.; Pei, X. Tantalum and its derivatives in orthopedic and dental implants: Osteogenesis and antibacterial properties. *Colloids Surf B Biointerfaces.* **2021**, *208*, 112055.
45. Horandghadim, N.; Khalil-Allafi, J.; Urgen, M. Effect of Ta(2) O(5) content on the osseointegration and cytotoxicity behaviors in hydroxyapatite-Ta(2)O(5) coatings applied by EPD on superelastic NiTi alloys. *Mater Sci Eng C Mater Biol Appl.* **2019**, *102*, 683-695.
46. Mei, S.; Yang, L.; Pan, Y.; Wang, D.; Wang, X.; Tang, T.; Wei, J. Influences of tantalum pentoxide and surface coarsening on surface roughness, hydrophilicity, surface energy, protein adsorption and cell responses to PEEK based biocomposite. *Colloids Surf B Biointerfaces.* **2019**, *174*, 207-215.
47. Li, R.; Liu, G.; Yang, L.; Qing, Y.; Tang, X.; Guo, D.; Zhang, K.; Qin, Y. Tantalum boride as a biocompatible coating to improve osteogenesis of the bionano interface. *J Biomed Mater Res A.* **2020**, *108*, 1726-1735.
48. Rouwkema, J.; Rivron, N. C.; van Blitterswijk, C. A. Vascularization in tissue engineering. *Trends Biotechnol.* **2008**, *26*, 434-441.
49. Cheng, S.; Ke, J.; Yao, M.; Shao, H.; Zhou, J.; Wang, M.; Ji, X.; Zhong, G.; Peng, F.; Ma, L.; Zhang, Y. Improved osteointegration and angiogenesis of strontium-incorporated 3D-printed tantalum scaffold via bioinspired polydopamine coating. *J Mater Sci Technol.* **2021**, *69*, 106-118.
50. Zhang, Y.; Zheng, Y.; Li, Y.; Wang, L.; Bai, Y.; Zhao, Q.; Xiong, X.; Cheng, Y.; Tang, Z.; Deng, Y.; Wei, S. Tantalum nitride-decorated titanium with enhanced resistance to microbiologically induced corrosion and mechanical property for dental application. *PLoS One.* **2015**, *10*, e0130774.
51. Zhu, Y.; Gu, Y.; Qiao, S.; Zhou, L.; Shi, J.; Lai, H. Bacterial and mammalian cells adhesion to tantalum-decorated micro-/nano-structured titanium. *J Biomed Mater Res A.* **2017**, *105*, 871-878.
52. Tokarski, A. T.; Novack, T. A.; Parvizi, J. Is tantalum protective against infection in revision total hip arthroplasty? *Bone Joint J.* **2015**, 97-B, 45-49.
53. Subramani, K.; Jung, R. E.; Molenberg, A.; Hammerle, C. H. Biofilm on dental implants: a review of the literature. *Int J Oral Maxillofac Implants.* **2009**, *24*, 616-626.
54. Harrison, P. L.; Harrison, T.; Stockley, I.; Smith, T. J. Does tantalum exhibit any intrinsic antimicrobial or antibiofilm properties? *Bone Joint J.* **2017**, 99-B, 1153-1156.
55. Wahl, P.; Sprecher, C. M.; Brüning, C.; Meier, C.; Milz, S.; Gautier, E.; Fintan Moriarty, T. Successful bony integration of a porous tantalum implant despite longlasting and ongoing infection: Histologic workup of an explanted shoulder prosthesis. *J Biomed Mater Res B Appl Biomater.* **2018**, *106*, 2924-2931.
56. Yang, C.; Li, J.; Zhu, C.; Zhang, Q.; Yu, J.; Wang, J.; Wang, Q.; Tang, J.; Zhou, H.; Shen, H. Advanced antibacterial activity of biocompatible tantalum nanofilm via enhanced local innate immunity. *Acta Biomater.* **2019**, *89*, 403-418.
57. Matharu, G. S.; Judge, A.; Murray, D. W.; Pandit, H. G. Do Trabecular metal acetabular components reduce the risk of rerevision after revision THA performed for periprosthetic joint infection? A study using the NJR data set. *Clin Orthop Relat Res.* **2019**, *477*, 1382-1389.
58. Wang, Q.; Zhang, H.; Gan, H.; Wang, H.; Li, Q.; Wang, Z. Application of combined porous tantalum scaffolds loaded with bone morphogenetic protein 7 to repair of osteochondral defect in rabbits. *Int Orthop.* **2018**, *42*, 1437-1448.
59. Bandyopadhyay, A.; Mitra, I.; Shivaram, A.; Dasgupta, N.; Bose, S. Direct comparison of additively manufactured porous titanium and tantalum implants towards in vivo osseointegration. *Addit Manuf.* **2019**, *28*, 259-266.
60. Wang, Q.; Qiao, Y.; Cheng, M.; Jiang, G.; He, G.; Chen, Y.; Zhang, X.; Liu, X. Tantalum implanted entangled porous titanium promotes surface osseointegration and bone ingrowth. *Sci Rep.* **2016**, *6*, 26248.
61. Wei, X.; Zhao, D.; Wang, B.; Wang, W.; Kang, K.; Xie, H.; Liu, B.; Zhang, X.; Zhang, J.; Yang, Z. Tantalum coating of porous carbon scaffold supplemented with autologous bone marrow stromal stem cells for bone regeneration in vitro and in vivo. *Exp Biol Med (Maywood).* **2016**, *241*, 592-602.
62. Fraser, D.; Mendonca, G.; Sartori, E.; Funkenbusch, P.; Ercoli, C.; Meirelles, L. Bone response to porous tantalum implants in a gap-healing model. *Clin Oral Implants Res.* **2019**, *30*, 156-168.
63. Hacking, S. A.; Bobyn, J. D.; Toh, K.; Tanzer, M.; Krygier, J. J. Fibrous tissue ingrowth and attachment to porous tantalum. *J Biomed Mater Res.* **2000**, *52*, 631-638.
64. Bobyn, J. D.; Stackpool, G. J.; Hacking, S. A.; Tanzer, M.; Krygier, J. J. Characteristics of bone ingrowth and interface mechanics of a new porous tantalum biomaterial. *J Bone Joint Surg Br.* **1999**, *81*, 907-914.
65. Sautet, P.; Parratte, S.; Mékidèche, T.; Abdel, M. P.; Flécher, X.; Argenson, J. N.; Ollivier, M. Antibiotic-loaded tantalum may serve as an antimicrobial delivery agent. *Bone Joint J.* **2019**, 101-B, 848-851.
66. Guo, X.; Chen, M.; Feng, W.; Liang, J.; Zhao, H.; Tian, L.; Chao, H.; Zou, X. Electrostatic self-assembly of multilayer copolymeric membranes on the surface of porous tantalum implants for sustained release of doxorubicin. *Int J Nanomedicine.* **2011**, *6*, 3057-3064.
67. Tanzer, M.; Karabasz, D.; Krygier, J. J.; Cohen, R.; Bobyn, J. D. The Otto Aufranc Award: bone augmentation around and within porous implants by local bisphosphonate elution. *Clin Orthop Relat Res.* **2005**, *441*, 30-39.
68. Zhou, R.; Xu, W.; Chen, F.; Qi, C.; Lu, B. Q.; Zhang, H.; Wu, J.;

Qian, Q. R.; Zhu, Y. J. Amorphous calcium phosphate nanospheres/polylactide composite coated tantalum scaffold: facile preparation, fast biomineralization and subchondral bone defect repair application. *Colloids Surf B Biointerfaces.* **2014**, *123*, 236-245.

69. Mrosek, E. H.; Schagemann, J. C.; Chung, H. W.; Fitzsimmons, J. S.; Yaszemski, M. J.; Mardones, R. M.; O'Driscoll, S. W.; Reinholz, G. G. Porous tantalum and poly-epsilon-caprolactone biocomposites for osteochondral defect repair: preliminary studies in rabbits. *J Orthop Res.* **2010**, *28*, 141-148.
70. Hua, L.; Lei, T.; Qian, H.; Zhang, Y.; Hu, Y.; Lei, P. 3D-printed porous tantalum: recent application in various drug delivery systems to repair hard tissue defects. *Expert Opin Drug Deliv.* **2021**, *18*, 625-634.
71. Rodeo, S. A.; Delos, D.; Weber, A.; Ju, X.; Cunningham, M. E.; Fortier, L.; Maher, S. What's new in orthopaedic research. *J Bone Joint Surg Am.* **2010**, *92*, 2491-2501.
72. Wu, Y.; Shi, X.; Zi, S.; Li, M.; Chen, S.; Zhang, C.; Xu, Y. The clinical application of customized 3D-printed porous tantalum scaffolds combined with Masquelet's induced membrane technique to reconstruct infective segmental femoral defect. *J Orthop Surg Res.* **2022**, *17*, 479.
73. Hua, L.; Lei, P.; Hu, Y. Knee Reconstruction Using 3D-Printed Porous Tantalum Augment in the Treatment of Charcot Joint. *Orthop Surg.* **2022**, *14*, 3125-3128.
74. Cheng, L.; Zhao, D.; Yang, L.; Li, J.; Ma, Z.; Wang, Z.; Tian, F.; Tian, S. The application of 3D printed customized porous tantalum acetabular patch for adult DDH hip reconstruction. *Zhonghua Guke Zazhi.* **2018**, *38*, 650-657.
75. Veillette, C. J.; Mehdian, H.; Schemitsch, E. H.; McKee, M. D. Survivorship analysis and radiographic outcome following tantalum rod insertion for osteonecrosis of the femoral head. *J Bone Joint Surg Am.* **2006**, *88 Suppl 3*, 48-55.
76. Liu, G.; Wang, J.; Yang, S.; Xu, W.; Ye, S.; Xia, T. Effect of a porous tantalum rod on early and intermediate stages of necrosis of the femoral head. *Biomed Mater.* **2010**, *5*, 065003.
77. Liu, Z. H.; Guo, W. S.; Li, Z. R.; Cheng, L. M.; Zhang, Q. D.; Yue, D. B.; Shi, Z. C.; Wang, B. L.; Sun, W.; Zhang, N. F. Porous tantalum rods for treating osteonecrosis of the femoral head. *Genet Mol Res.* **2014**, *13*, 8342-8352.
78. Zhang, X.; Wang, J.; Xiao, J.; Shi, Z. Early failures of porous tantalum osteonecrosis implants: a case series with retrieval analysis. *Int Orthop.* **2016**, *40*, 1827-1834.
79. Tanzer, M.; Bobyn, J. D.; Krygier, J. J.; Karabasz, D. Histopathologic retrieval analysis of clinically failed porous tantalum osteonecrosis implants. *J Bone Joint Surg Am.* **2008**, *90*, 1282-1289.
80. Zhao, D.; Zhang, Y.; Wang, W.; Liu, Y.; Li, Z.; Wang, B.; Yu, X. Tantalum rod implantation and vascularized iliac grafting for osteonecrosis of the femoral head. *Orthopedics.* **2013**, *36*, 789-795.
81. Zhao, D.; Liu, B.; Wang, B.; Yang, L.; Xie, H.; Huang, S.; Zhang, Y.; Wei, X. Autologous bone marrow mesenchymal stem cells associated with tantalum rod implantation and vascularized iliac grafting for the treatment of end-stage osteonecrosis of the femoral head. *Biomed Res Int.* **2015**, *2015*, 240506.
82. Sculco, T. P. The acetabular component: an elliptical monoblock alternative. *J Arthroplasty.* **2002**, *17*, 118-120.
83. Macheras, G.; Kateros, K.; Kostakos, A.; Koutsostathis, S.; Danomaras, D.; Papagelopoulos, P. J. Eight- to ten-year clinical and radiographic outcome of a porous tantalum monoblock acetabular component. *J Arthroplasty.* **2009**, *24*, 705-709.
84. Macheras, G. A.; Papagelopoulos, P. J.; Kateros, K.; Kostakos, A. T.; Baltas, D.; Karachalios, T. S. Radiological evaluation of the metal-bone interface of a porous tantalum monoblock acetabular component. *J Bone Joint Surg Br.* **2006**, *88*, 304-309.
85. Garbuz, D. S. Revision total hip: a novel modular cementless acetabular system for reconstruction of severe acetabular bone loss. *Oper Tech Orthop.* **2004**, *14*, 117-120.
86. Sporer, S. M.; Paprosky, W. G. The use of a trabecular metal acetabular component and trabecular metal augment for severe acetabular defects. *J Arthroplasty.* **2006**, *21*, 83-86.
87. Malkani, A. L.; Price, M. R.; Crawford, C. H., 3rd; Baker, D. L. Acetabular component revision using a porous tantalum biomaterial: a case series. *J Arthroplasty.* **2009**, *24*, 1068-1073.
88. Löchel, J.; Janz, V.; Hipfl, C.; Perka, C.; Wassilew, G. I. Reconstruction of acetabular defects with porous tantalum shells and augments in revision total hip arthroplasty at ten-year follow-up. *Bone Joint J.* **2019**, *101-b*, 311-316.
89. Hu, B.; Chen, Y.; Zhu, H.; Wu, H.; Yan, S. Cementless porous tantalum monoblock tibia vs cemented modular tibia in primary total knee arthroplasty: a meta-analysis. *J Arthroplasty.* **2017**, *32*, 666-674.
90. Hayakawa, K.; Date, H.; Tsujimura, S.; Nojiri, S.; Yamada, H.; Nakagawa, K. Mid-term results of total knee arthroplasty with a porous tantalum monoblock tibial component. *Knee.* **2014**, *21*, 199-203.
91. Wang, F.; Chen, H.; Yang, P.; Muheremu, A.; He, P.; Fan, H.; Yang, L. Three-dimensional printed porous tantalum prosthesis for treating inflammation after total knee arthroplasty in one-stage surgery - a case report. *J Int Med Res.* **2020**, *48*, 300060519891280.
92. De Martino, I.; D'Apolito, R.; Sculco, P. K.; Poultsides, L. A.; Gasparini, G. Total knee arthroplasty using cementless porous tantalum monoblock tibial component: a minimum 10-year follow-up. *J Arthroplasty.* **2016**, *31*, 2193-2198.
93. Sambaziotis, C.; Lovy, A. J.; Koller, K. E.; Bloebaum, R. D.; Hirsh, D. M.; Kim, S. J. Histologic retrieval analysis of a porous tantalum metal implant in an infected primary total knee arthroplasty. *J Arthroplasty.* **2012**, *27*, 1413.e5-9.
94. Levine, B.; Sporer, S.; Della Valle, C. J.; Jacobs, J. J.; Paprosky, W. Porous tantalum in reconstructive surgery of the knee: a review. *J Knee Surg.* **2007**, *20*, 185-194.
95. Potter, G. D., 3rd; Abdel, M. P.; Lewallen, D. G.; Hanssen, A. D. Midterm results of porous tantalum femoral cones in revision total knee arthroplasty. *J Bone Joint Surg Am.* **2016**, *98*, 1286-1291.
96. Kamath, A. F.; Lewallen, D. G.; Hanssen, A. D. Porous tantalum metaphyseal cones for severe tibial bone loss in revision knee arthroplasty: a five to nine-year follow-up. *J Bone Joint Surg Am.* **2015**, *97*, 216-223.
97. Rodríguez-Merchán, E. C.; Gómez-Cardero, P.; Encinas-Ullán, C. A. Management of bone loss in revision total knee arthroplasty: therapeutic options and results. *EFORT Open Rev.* **2021**, *6*, 1073-1086.
98. Kamath, A. F.; Gee, A. O.; Nelson, C. L.; Garino, J. P.; Lotke, P. A.; Lee, G. C. Porous tantalum patellar components in revision total knee arthroplasty minimum 5-year follow-up. *J Arthroplasty.* **2012**, *27*, 82-87.
99. Hanc, M.; Fokter, S. K.; Vogrin, M.; Molicnik, A.; Recnik, G. Porous tantalum in spinal surgery: an overview. *Eur J Orthop Surg Traumatol.* **2016**, *26*, 1-7.
100. Fernández-Fairen, M.; Alvarado, E.; Torres, A. Eleven-year follow-up of two cohorts of patients comparing stand-alone porous tantalum cage versus autologous bone graft and plating in anterior cervical fusions. *World Neurosurg.* **2019**, *122*, e156-e167.

101. Mastronardi, L.; Roperto, R.; Cacciotti, G.; Calvosa, F. Anterior cervical fusion with stand-alone trabecular metal cages to treat cervical myelopathy caused by degenerative disk disease. observations in 88 cases with minimum 12-month follow-up. *J Neurol Surg A Cent Eur Neurosurg*. **2018**, *79*, 496-501.
102. Lebhar, J.; Kriegel, P.; Chatellier, P.; Breton, Y.; Ropars, M.; Huten, D. Tantalum implants for posterior lumbar interbody fusion: a safe method at medium-term follow-up? *Orthop Traumatol Surg Res.* **2020**, *106*, 269-274.
103. Li, N.; Hu, W. Q.; Xin, W. Q.; Li, Q. F.; Tian, P. Comparison between porous tantalum metal implants and autograft in anterior cervical discectomy and fusion: a meta-analysis. *J Comp Eff Res.* **2019**, *8*, 511-521.
104. Adukia, V.; Mangwani, J.; Issac, R.; Hussain, S.; Parker, L. Current concepts in the management of ankle arthritis. *J Clin Orthop Trauma.* **2020**, *11*, 388-398.
105. Horisberger, M.; Paul, J.; Wiewiorski, M.; Henninger, H. B.; Khalifa, M. S.; Barg, A.; Valderrabano, V. Commercially available trabecular metal ankle interpositional spacer for tibiotalocalcaneal arthrodesis secondary to severe bone loss of the ankle. *J Foot Ankle Surg.* **2014**, *53*, 383-387.
106. Tiusanen, H.; Kormi, S.; Kohonen, I.; Saltychev, M. Results of trabecular-metal total ankle arthroplasties with transfibular approach. *Foot Ankle Int.* **2020**, *41*, 411-418.
107. Sundet, M.; Johnsen, E.; Eikvar, K. H.; Eriksen, M. L. Retrograde nailing, trabecular metal implant and use of bone marrow aspirate concentrate after failed ankle joint replacement. *Foot Ankle Surg.* **2021**, *27*, 123-128.
108. Onggo, J. R.; Nambiar, M.; Phan, K.; Hickey, B.; Galvin, M.; Bedi, H. Outcome after total ankle arthroplasty with a minimum of five years follow-up: a systematic review and meta-analysis. *Foot Ankle Surg.* **2020**, *26*, 556-563.
109. Epperson, R. T.; Barg, A.; Williams, D. L.; Saltzman, C. L. Histological analysis of a retrieved porous tantalum total ankle replacement: a case report. *JBJS Case Connect.* **2020**, *10*, e0379.
110. Zhao, D. W.; Ma, Z. J.; Wang, T. N.; Liu, B. Y. Biocompatible porous tantalum metal plates in the treatment of tibial fracture. *Orthop Surg.* **2019**, *11*, 325-329.
111. Li, F.; Jiang, C. Trabecular metal shoulder prosthesis in the treatment of complex proximal humeral fractures. *Int Orthop.* **2013**, *37*, 2259-2264.
112. Chen, R. E.; Mannava, S.; Miller, R. J.; Voloshin, I. Comparison of mid-term outcomes of total shoulder arthroplasty for B2 and A glenoids treated with trabecular metal glenoid components. *Semin Arthroplasty.* **2020**, *30*, 326-332.
113. Sasanuma, H.; Iijima, Y.; Saito, T.; Kanaya, Y.; Yano, Y.; Fukushima, T.; Nakama, S.; Takeshita, K. Clinical results of reverse shoulder arthroplasty for comminuted proximal humerus fractures in elderly patients: a comparison between nonporous stems versus trabecular metal stems. *JSES Int.* **2020**, *4*, 952-958.

Received: November 16, 2022
Revised: August 3, 2023
Accepted: August 30, 2023
Available online: September 28, 2023