

The clinical application of porous Tantalum and its new development for bone tissue engineering

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Abstract

Porous tantalum (Ta) is a promising biomaterial and has been applied in orthopedics and dentistry for nearly two decades. The high porosity and interconnected pore structure of porous Ta promise fine bone ingrowth and new bone formation within the inner space, which further guarantee rapid osteointegration and bone-implant stability in long term. Porous Ta has high wettability and surface energy that can facilitate adherence, proliferation and mineralization of osteoblasts. Meanwhile, low elastic modulus and high friction coefficient of porous Ta can effectively avoid stress shield effect, minimize marginal bone loss and ensure primary stability. Accordingly, the satisfactory clinical application of porous Ta based implants or prostheses are mainly derived from its excellent biological and mechanical properties. With the advent of additive manufacturing, personalized porous Ta based implants or prostheses have shown their clinical value in the treatment of individual patient who need specially designed implant or prosthesis. In addition, many modification methods have been introduced to enhance the bioactivity and antibacterial property of porous Ta with promising *in vitro* and *in vivo* research results. In any case, choosing suitable patients is of great importance to guarantee surgical success after porous Ta insertion.

Key words: porous tantalum; clinical application; additive manufacturing; surface modification; bone tissue engineering

1. Introduction

Named from Greek mythological figure -Tantalus[1], tantalum or Ta is a rare, rigid and ductile metal element with extremely high melting point (3017°C)[2] and density (16.6g/cm³) [3, 4]. Ta has excellent biocompatibility and corrosion resistance, has been used as pacemaker electrodes, suture wire, cranioplasty plate, radiopaque marker, foil and mesh for never repair since 1940s[5]. In addition, Ta has been used as single or composite coating material to modify the biological and mechanical properties of pure titanium(Ti)[6-8], Ti alloy (Ti6Al4V)[9], polyetheretherketone (PEEK) [10], cobalt-chromium (CoCr) alloy [11, 12], magnesium-based alloy [13], pure Fe [14] and 316L stainless steel [15]. Recently, the advent of Ti-Ta alloy with different Ta element content indicates a novel way to fabricate implants for bone defects restoration with improved mechanical strength, satisfactory elastic modulus and biological properties compared to pure Ti and Ti alloy[2, 16, 17].

Though lacking of intrinsic antibacterial property[18], Ta has a lower bacterial adhesion level and colonization compared to titanium (Ti) and stainless steel due to the spontaneously formed oxide surface layer (Ta₂O₅) [19, 20]. The Ta₂O₅ layer also has

been proved to facilitate the deposition of bone-like apatite coating in simulated body fluid (SBF) [21], and further accelerate the adherence of osseous and soft tissues [22]. Moreover, nanoparticles released from Ta implants have been certified to stimulate the proliferation of osteoblasts via autophagy, and the osteogenic process can further be enhanced by autophagy inducer [23]. Despite the osteogenic signaling pathways of Ta have yet been fully explicated, several researches have focused on TGF- β /Smad3/Runx2[24], BMP2/Smad1/Runx2[25], Wnt/ β -catenin/Runx2[24, 26], and Integrin α 5 β 1/ERK1/2/Runx2 pathway[27, 28] that may involve in the osteogenic effects of Ta. It is also reported that Ta can enhance the osteogenesis of diabetic rabbits by suppressing the activation of ROS-mediated P38 MAPK signaling pathway [29]. Furthermore, Ta upregulate the expression level of osteoprotegerin (OPG) and reduce that of RANKL, which means Ta also can inhibit the activity of osteoclasts [25].

Compared to its solid counterpart, currently commercialized porous Ta possesses modified physical properties including high porosity (range from 75% to 85%), dodecahedral cell structure and pores size ranging from 400 to 600 μ m, which greatly facilitate bone and soft tissue ingrowth due to its extensively three-dimensional inner space [30, 31]. The mechanical properties of porous Ta are also improved to be more suitable for bone-tissue regeneration especially for load-bearing parts of the body due to its elastic modulus (3 GPa) is much more comparable with human bones[22, 30]. The lower elastic modulus of porous Ta is of great importance to proportionally distribute load stress to adjacent osseous tissues, minimize stress shield effect, prevent bone resorption, and even preserve the adjacent bone stock [32]. In addition, the high friction coefficient of porous Ta also promise the primary stability for the porous Ta based implants or prostheses [33].

Owing to the inherent high wettability and surface energy, porous Ta can facilitate the adhesion, differentiation and spread of osteoblasts[34] [35, 36], chondrocytes [37] as well as vascularized fibrous tissues [38] and tendon [39]. Meanwhile, the high porosity of porous Ta promises its desirable permeability for vascularization and nutrients flow, which can guarantee rapid osteointegration at early stage [40]. And bone ingrowth can be found within the pores of porous Ta as early as 4 weeks after implantation [36]. Many *in vivo* researches also have highlighted its early osteointegration and evidenced bone in-growth within the inner pores with Haversian remodeling in the long term [22, 36, 41, 42]. *In vitro*, after cultured on the porous Ta, osteoblasts obtained from old female patients (>60 years) showed better proliferation and osteogenesis than those cultured on Ti fiber mesh [43], indicating the potential efficacy of porous Ta for the treatment of patients suffered from osteoporosis.

The commercially available porous Ta implants are fabricated via Chemical Vapor Deposition (CVD) by Zimmer Biomet Inc. (IN, USA), also known as trabecular metal which resembles cancellous bone due to its microstructure[30]. At present, additive manufacturing (AM), also known as 3-Dimensional printing or rapid prototyping has been exploited to fabricate porous tantalum scaffolds or implants. The procedures of AM technology mainly include electron beam melting (EBM), laser engineering net shaping (LENS), and selective laser melting (SLM). Compared with CVD or other traditional subtractive manufacturing, AM exhibits superior performance with satisfactory cost-efficiency, less time and material consuming[44]. With the help of AM technology, both the macrostructure and microstructure of porous Ta can be precisely controlled during the producing process based on the designing parameters. The Additive manufactured porous Ta scaffolds also show satisfactory fatigue strength and load-bearing capacity[45]. Moreover, many modification methods have been employed

to enhance the bioactivity and antibacterial property of porous Ta for its future application in bone tissue engineering.

So far, porous Ta based implants or prostheses have been extensively applied in orthopedics and dentistry (see Figure 1). Therefore, the aim of this literature is to review the clinical application of porous Ta based implants or prostheses which have been implemented in orthopedics and dentistry, and summarize new manufacturing and modification methods for this promising porous biomaterial.

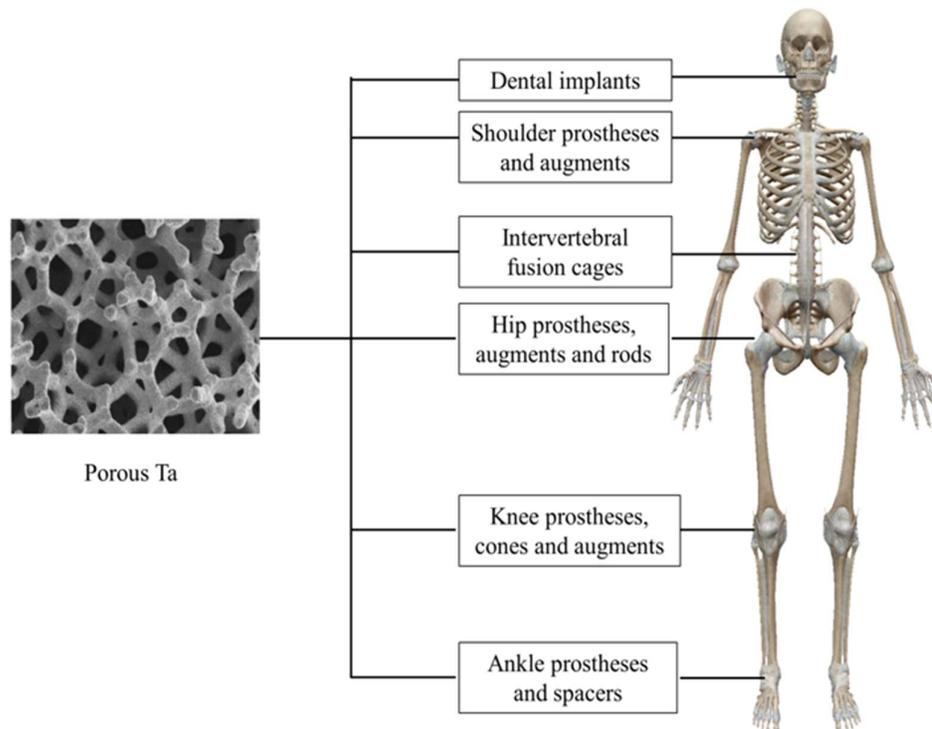


Figure 1: Porous Ta has been extensively applied in different parts of human body for restoration surgery due to its superior biological and mechanical properties.

2. Clinical application of porous Ta in orthopedics and dentistry

2.1 Femoral head osteonecrosis

Osteonecrosis of femoral head can be a disaster disease for the young and middle-aged patients who are physically active [46, 47]. Therefore, appropriate measures should be taken at the early stage to preserve femoral head before the final collapse of femoral head and subchondral plate.

Core decompression has been applied in the salvage of femoral head for many years, but the lack of mechanical support to subchondral bone after debridement of necrotic bone may further results in collapse of the head [48]. Meanwhile, in their histopathology study, Gonzalez Del Pino et al.[49] found the new bone formation originated mainly from the host bones rather than the vascularized grafts. In this regard, as a reasonable substitute for vascularized fibular autografts, porous Ta rod has been

used as a supplement approach to sustain the bony defect portion after core decompression [50].

Primarily designed to provide structure sustaining for the subchondral plate and stimulate osteogenesis of the host bone, porous Ta rod has been proved to alleviate the deterioration of femoral head necrosis and postpone the final conversion to total hip arthroplasty in the majority of publications for the early or intermediate stage patients [50-53]. Though the efficacy of this tantalum rod remains controversial in the long-term [54] and remove of the rod would be an obstacle when conversion to total hip arthroplasty [55]. The survival rates after porous Ta rod insertion are impacted by multi-factors including stage of the disease, corticosteroid usage, osteonecrosis lesion volume and location, bone marrow edema, and joint effusion [56, 57]. The presence of bone marrow edema has been proved to be a poor prognostic factor of femoral head osteonecrosis and also a predictor of conversion to total hip arthroplasty (THA). And patients accompanied by bone marrow edema had significantly higher possibility to resort to THA eventually [57].

It should be noted that the diameter of porous Ta rod is only 10 mm, which confines the supporting area of the rod; if the lesion size was larger than that diameter, collapse would occur at other areas [58]. Moreover, the histopathological analysis of 15 retrieved porous Ta rods revealed 1.9% bone ingrowth and mechanical support for subchondral bone were proved to be insufficient [59]. Thus, improvement of implant design and surgical technique should be processed, and the patients' necrotic stages should also be needed to be scrutinized before the surgical procedure was taken [60]. Accordingly, many modified surgical techniques have been introduced to enhance the osteogenesis ability of porous Ta rod, including combined with bone marrow aspirated from iliac crest [61], or with vascularized bone grafting alone [62], or with bone marrow mesenchymal stem cells (BMMSCs) and vascularized autografts [63]. However, longer-term follow-up clinical trials are still desired to verify the efficacy of these modified methods.

2.2 Hip arthroplasty

The porous Ta acetabular cup for primary THA is fabricated by directly compressing the ultra-high molecular polyethylene into an elliptical porous Ta shell. This kind of monoblock acetabular component design has theoretically diminished the occurrence of backside wear and the absence of screw holes shuts the access of polyethylene wear debris infiltrating into the bone-implant interface, which has long been regarded as an initiating factor resulting in aseptic loosening of the cup [64]. The porous Ta shell with low elastic modulus, high friction coefficient and excellent osteoconductivity can help to preserve or even increase the bone stock of adjacent acetabulum and facilitate the revision surgery if it is necessary [65].

In a preclinical research, 22 porous Ta acetabular components were exploited in canine model [35]. Results had revealed that the bone in-growth depth of the 22 cups ranged from 0.2 to 2 mm after 6 months. And the average bone ingrowth in total sections was 16.8% and 25.1% in the periphery, both were better than the results of another canine model study in which bone ingrowth in titanium fiber and Co-Cr was 21.5% and 13.4% respectively [66]. Clinically, 151 hips were followed up for 8-10 years post primary THA in a prospective study [67]. Although periacetabular gaps with lengths ranging from 1 to 5 mm could be found in 25 hips at early stage, those gaps disappeared after 24 weeks. The follow-up radiograph verified the absence of radiolucency, osteolysis of the adjacent bone, polyethylene wear debris and cup

loosening. All these indicated the designing advantages of the porous Ta cup. Substantial bone deposition could be found on the surface of a retrieved acetabular component after 50 months due to dislocation in this study. But the lack of screw holes of the cup may hampered the direct observation of dome contact during surgery and the final seating of the cup into acetabular socket could not accurately ensured [67].

As for revision THA, it is a surgical challenge to reconstruct acetabulum with huge bone defects and to restore primary stability, rotational center and maximal bone-implant contact [68]. Porous Ta acetabular prostheses have been revealed as an optimal option to cope with these formidable missions [69-73]. The modular design of the porous Ta revision prosthesis provides augment or buttress sections to be screwed onto the supra-acetabulum for bone defects reconstruction, after that the elliptical cup is implanted in acetabular socket against the section with cement laying in the interface of the two components [74]. Many short and midterm studies have shown promising results of the modular porous Ta acetabular shell and augment in the treatment of acetabular dome defect with or without osteolysis of ischium, teardrop and Kohler line disruption (Paprosky type II or III) [71, 73, 75-80]. A ten-year follow-up after revision surgery with porous Ta shell and augment implantation was conducted by Löchel et al [81]. The survival rate of 51 patients (53 hips) who had completed the follow-up was 92.5% with a significant increasing in Harris Hip Score (55 before surgery Vs 81 post surgery) after the revision surgery. Meanwhile, the authors strongly recommended the application of screws toward the load transferring and inferior direction in every patient with acetabular defects to stabilize the shell and augment, diminish the fretting at the interface of shell-host bone or shell-augment and guarantee the primary stability for long-term survival rate [81]. In addition, porous Ta acetabular implants and augments were suggested in the reconstruction of hip joint after resection of peri-acetabular tumors for their satisfactory clinical results at early stage [82]. The irradiated pelvis was reported to be always associated with high aseptic loosening rate of acetabular components [83-85]. Even so, porous Ta cups still obtained satisfactory results in THA treatment of irradiated pelvis owing to their high friction coefficient and porous microstructure, as well as rapid bone in-growth rate [83-85]. However, it is imperative to note that transverse acetabulum fracture may occur during or after the revision surgery if excessive reaming is performed so as to insert large cups (average 58 mm) in the operation [86, 87].

2.3 Knee arthroplasty

Porous Ta prosthesis for knee primary and revision reconstruction comprises of monoblock tibial component, tibial or femoral cone and augment, as well as patella prosthesis. The design of monoblock tibial component for primary arthroplasty is similar to that of monoblock acetabular component, with the polyethylene directly compressed into a porous Ta baseplate, which also eliminate the potential occurrence of wear debris infiltrating into bone-implant interface. The mechanical and biological properties of porous Ta guarantee the primary stability of the tibial component and ensure its long-term survival rate [88]. Several short and long term results have shown encouraging efficacy of this cemented or uncemented monoblock tibial component for the treatment of relative young and active patients [89-94]. A histological analysis of retrieved porous Ta tibial component from a chronically infected knee prosthesis revealed significant bone in-growth in the posts and post-baseplate interface rather than baseplate, suggesting fine bone-implant integration could still be obtained even in the infected environment [95]. However, cautions should be taken to patients who had

heavy weight (average 241.9 lbs) and tall height (average 71.8 inch) and had received total knee arthroplasty (TKA) with cementless porous Ta tibial prostheses before, as this patients group may easily encounter early medial collapse due to the overload cyclically posed on the medial portion of the tibial prosthesis [96].

Severe distal femoral and proximal tibial bone defects are the greatest challenge in revision total knee arthroplasty. Without adequate bony support and inferior bony structure, collapse of tibial or femoral component will definitely happen.. Therefore, porous Ta cones for substitution of tibial and femoral metaphyseal bone defects have been introduced to function as structural graft, to enhance bone stock, and to regain normal articular alignment with multiple flexibilities for different sizes and positions of bone loss [88, 97]. Reasonable results of a 5-year study reported by Potter et al. [98] indicating porous Ta femoral cones could effectively fill the metaphyseal defects of distal femur and sustain the femoral component after revision TKA. Another five to nine years follow-up study supported the efficient application of porous Ta tibial cones for restoration of huge osseous loss and facilitated early weight-bearing [99]. Though long-term and comparison analysis are still needed to further verify the viability of this porous cones for massive metaphysis defects reconstruction. And the high price of per cone (approximately \$4,000) would impede its clinical application in large scale [100].

Restoring normal function and structure of patellofemoral joint will be an integral portion in TKA or revision TKA if the extensor mechanism has been impaired due to patellar resection or severe osseous deficiency. Owing to the capability of favoring soft tissue and bone ingrowth [36, 38], porous Ta patellar prosthesis has been used to reconstruct the fulcrum role of patella [101]. However, the stability of this novel patellar prosthesis depends mainly on the residual bone stock of patella, rather than soft tissue [102]. Moreover, abundant bone-implant contact and blood supply to the residual patella are critical factors for the long term success of porous Ta patellar prosthesis [103]. Therefore, prudent selection of proper patients should be the prior step before definite surgery to be performed, so as to avoid the recurrence of complications such as persistent pain, weakened extensor mechanism, and patellar shell fracture.

2.4 Shoulder arthroplasty

Glenoid component loosening is always a disturbing complication of total shoulder arthroplasty (TSA) or reverse total shoulder arthroplasty (RTSA) despite various methods have been implemented to address it [104-108]. Based on the successful experience in hip and knee arthroplasty, porous Ta baked monoblock glenoid component has been introduced for TSA [109] and RTSA [110], utilizing the properties of rapid osteointegration and high friction coefficient of porous Ta which can elongate survivorship of the shoulder prosthesis in the long-run.

Budge et al. [109] reported prosthetic fracture of the first generation of porous Ta glenoid component occurred in 4 of 19 patients after 30 months. All the 4 glenoid component fractures appeared at interface of keel and metal plate, indicating a combined effort of cyclic loading and insufficient bony support to glenoid portion of the prosthesis that finally ignited the fatigue failure at the junction of keel-metal plate [109]. Therefore, emphases should be placed on gaining a compacted press-fit pattern of the metal component in surgery [111]. Reinforced with anterior-posterior keels and extended interdigitating at the interface of polyethylene tray and porous Ta plate, the redesigned second generation of porous Ta glenoid prosthesis is introduced to cope with the annoying keel-glenoid plate junction fracture frequently occurred in the first generation [112].

Improved clinical performance of the second generation porous Ta glenoid component were revealed in 40 patients who were followed up for 38 months post TSA [112]. Significant progress of shoulder function scores were found in all the 40 patients without conspicuous prostheses loosening, migration or fracture [112]. After 76 shoulders were replaced with porous Ta glenoid components and followed up for average 43.2 months, Panti et al. [113] also reported satisfactory clinical results in terms of improved range of motion, pain relieving and advanced function scores with the absence of severe complications such as implants fracture or loosening. The mechanism of successful results obtained in the two aforementioned studies mainly depended on the amplified cruciform pegs which guaranteed the compact press-fit mechanism of the glenoid component in host bone without cement and effectively withstood the eccentric loading force loading on it. Meanwhile, the expanded interlocking between polyethylene tray and porous metal plate helped to resist debonding force and diminish possibility of potential glenoid component fracture.

Nevertheless, it should be noted that the monoblock porous Ta glenoid component may cause trouble when revision TSA is to be performed, for it would be difficult to be removed due to stable bone-implant interlocking and substantial bone ingrowth even associated with infected host bone [114] and may subsequently result in central osseous defect or scapular fracture [111]. Still, accumulated metallic debris deposition derived from porous Ta component with a time-depending pattern can still be found after anatomic shoulder arthroplasty, which means mechanical failure remains a threat for long-term survival rate and regular radiographic follow-up should be implemented to verify the stability of the porous Ta glenoid component [115].

Superior migration of greater tuberosity is a critical factor which often results in surgical failure after shoulder hemiarthroplasty for the treatment of complex proximal humeral fracture. The migrated great tuberosity is the main cause of subacromial impingement, shoulder joint stiffness and persistent pain [116]. Humeral stem prostheses fabricated with porous Ta have been proposed to accelerate anatomic union of greater tuberosity which can effectively minimize the occurrence of greater tuberosity malposition after surgery and ensure the surgical efficacy eventually [117, 118].

In addition, porous Ta glenoid augments have recently been used to correct glenoid retroversion in 10 patients with satisfactory efficacy of repositioning the retroverted glenoid to neutral position [119]. Glenoid retroversion caused by dysplasia or degenerative deformity can lead to eccentric loading, permanent posterior subluxation of humeral head and the disaster prosthetic failure [119]. Therefore, porous Ta glenoid augment can be an optimal approach to correct glenoid deformity, though more evidences are desired to verify its exact efficacy.

2.5 Spine intervertebral fusion

The efficacy of porous Ta cage applied in anterior cervical spine fusion has been confirmed in a prospective randomized controlled clinic trial conducted by Fernández-Fairen et al [120]. Compared with traditional autologous iliac bone graft combined with anterior plating, porous Ta cage insertion group showed equivalent fusion rate (89% Vs 85%) and post-surgery stability at the end point of 2-year follow-up, but additional fixation and graft harvesting related injury were no longer entailed [120]. After 11 years of follow-up, the clinical and radiological results of patients who had received single porous Ta cage insertion for interbody fusion remained satisfactory despite implants subsidence presented within 2-3mm without

significant complication in 12 patients [121]. And several observational studies had also affirmed the efficacy of porous Ta in terms of interbody fusion rate, low complication rate and improved short or long term post-surgery evaluation scores including SF-36, neck disability index (NDI) and visual analog score (VAS) [122-124].

On the contrary, another prospective randomized multicenter study showed a frustrating fusion rate of stand-alone porous Ta device insertion group compared to iliac crest autograft group (44% Vs 100%) after 2-year follow-up [125]. And the histological analysis of 2 retrieved tantalum blocks from patients diagnosed as nonunion at 6-month and 12-month respectively revealed substantial fibrous in-growth instead of bony tissues [125]. Similarly, Löfgren et al. [126] found a significantly lower fusion rate of porous Ta than iliac crest bone grafting (69% Vs 92%). Considering potential nonunion, Wigfield et al. [127] terminated their prospective study prematurely due to radiolucent lines appeared at the anterior-inferior border of porous Ta implants in 4 patients either implanted with blocks or rings at 6 weeks, though the lucent lines disappeared 12 months post-surgery and final outcomes of porous Ta insertion group were better than autologous bone grafted group.

Accordingly, two Meta-analyses [128, 129] have recently analyzed the intro-operation and post-surgery parameters including operating time, blood loss, hospital stay, fusion rate, NDI and VAS scores, as well as satisfaction and complication rates of relative clinical trials. Through the two Meta-analyses, porous Ta implants possess the same efficacy and safety in the surgical treatment of anterior cervical degenerative disc diseases as autologous iliac bone grafting which has long been regarded as gold standard [128, 129]. However, more randomized controlled trials with large samples are still desired to reinforce the clinical evidences of porous Ta implants.

In addition to high friction coefficient, porous Ta can offer adapt circumstance for rapid bone ingrowth [31], which further guarantees its long-term stability for lumbar intervertebral fusion either with or without the augment of pedicle screws [130]. Lequin et al. [131] used standalone porous Ta cages in the treatment of 26 patients suffered from recurrent lumbar disc herniation. Though moderate satisfactory clinical results were revealed and significant relieved back and leg pain was only reported in 46% of patients, 85% of patients had possessed remarkable improvement in their working-status post-surgery 1 year [131]. Meanwhile, Lebhar et al. [132] and Butler et al. [133] respectively reported reliable clinical, functional and radiographic results after the application of porous Ta implant for lumbar intervertebral fusion in their retrospective cohort studies.

Furthermore, in a randomized controlled trail (RCT), 80 patients were either enrolled into standalone porous Ta cage fusion group or pedicle screws supplemented group [134]. Similar clinical evaluation results including Oswestry Disability Index (ODI), VAS and SF-36 scores were revealed at 2-year follow-up point [134]. And equivalent X-ray results of both groups evaluated at 6-year follow-up proposed that porous Ta standalone fashion could provide stability for lumbar spine interbody fusion without additional fixation or bone grafting [134]. However, RCTs are still rare used to definitely corroborate the clinical value of porous Ta cages for lumbar spine fusion surgery either used as standalone fashion or augmented with posterior screws. And the radiopaque property of tantalum makes the radiographic examination of intervertebral bone fusion rate difficult.

2.6 Ankle arthrodesis and arthroplasty

Just as femoral head osteonecrosis, the end-stage ankle arthritis can also be a

catastrophic disability disease for the younger and active patients [135, 136]. Therefore, surgical intervention e.g., ankle arthrodesis and total ankle arthroplasty should be taken into consideration when conservative methods are failed,

Regarded as promising alternative to traditional bone autograft or allograft, porous Ta spacer has been applied in ankle arthrodesis without the limits of size, volume and source [137-140]. And the expenditure of single porous Ta spacer (approximately \$989.5-1000) has been reported to be comparable with iliac crest autograft (approximately \$600-700) and allograft (approximately \$850) to some extent; however the latter two may take more time for preparation during the surgery [137-139]. Porous Ta spacer will be an optimal choice for reconstruction surgery, which is especially suitable for huge bone defect [141, 142]. Because it has adequate structural strength to maintain the restored height and angular correction of ankle joint until the appearance of osseous fusion between porous Ta spacer and adjacent bony tissues [30, 138], which is significantly different from bone autograft or allograft, either of which may collapse due to absorption after implantation [41, 137, 143]. Moreover, just as cancellous bone, porous Ta spacer provide capacious space and osteoconductive environment for vascularized bone tissue ingrowth, obviating autograft related harvest lesions [144, 145] and allograft related infectious diseases [140].

The clinic results of porous Ta spacers used for the salvage of failed total ankle arthroplasty are also favorable [142, 143, 146]. More often, accompanied by nonunion, leg shortening, infection or even severe bone defect after debridement, failed total ankle arthroplasty can be a challenge to be reasonably addressed [143, 147]. To enhance the fusion efficiency of porous Ta spacer, Sundet et al. [146] combined the use of retrograde nailing, porous Ta spacer and osteoinductive pad augmented with autologous bone marrow concentrate for revision surgery of 30 patients (31 ankles) with failed total ankle arthroplasty. The mean fusion rate at the average 23-month follow-up was 93.5%, and the vast majority of patients were satisfied with the surgery in terms of pain relief and improved activity, though additional expenditure were entailed in this clinic trial [146]. Similarly, Kreulen et al. [142] introduced a new surgical strategy for reconstruction surgery of 2 patients with failed total ankle arthroplasty and 4 patients with ankle collapse post infection. In this study, porous Ta spacers were also augmented with autologous bone marrow obtained by Reamer/Irrigator/Aspirator technique from femoral marrow cavity and fixed with tibiotalar calcaneal nail, bone morphogenetic protein 2 (BMP-2) or platelet derived growth factor was further supplemented to boost bony fusion. With the help of this novel method, thorough osseous fusion at the implant-bone interface appeared at early stage of 4-6 weeks post-surgery and no failure cases were observed [142]. In contrast, Aubret et al. [147] reported disappointing outcomes after the insertion of porous Ta spacers. Even augmented with iliac crest autograft and allograft bone chips for revision of failed total ankle arthroplasty in 10 patients, 2 patients had failed integration of porous Ta spacers, 1 patient presented as talocrural joint nonunion and 3 patients needed secondary revision surgery due to severe pain. However, the main reason of these failed cases was supposed to be the weak fixation strength provided by nails compared with 6.5mm screws [138] or reconstruction plates [143].

Despite reported as lower survival rate than hip and knee arthroplasty [148-150], total ankle arthroplasty (TAA) has been suggested to preserve the mobility of ankle joint and normal gait instead of being fused with triple arthrodesis which has long been considered as gold standard for the treatment of end-stage ankle arthritis.

A newly designed porous Ta based total ankle prosthesis has been approved by Food and Drug Administration in 2012 and marketed by Zimmer Biomet Inc [151, 152].

Combined with the use of porous Ta based ankle prosthesis in TAA, promising prognosis can be foreseeable in terms of pain relieving and functional improvement in short-term even without supplemented with cement augmentation, for the stability of tibial and talar components mainly depend on bony interlocking between the porous Ta base and host bone [151-157]. Moreover, the pattern of porous Ta bases of the two components resembles that of subchondral bone of tibia and talus and can distribute loading stress rationally and diminish the occurrence of peri-implant osteolysis, which often resulted in aseptic loosening of the implants [152, 158]. This novel ankle prosthesis is implanted through lateral approach associated with distal fibular osteotomy which theoretically offer direct exposure for both sagittal and coronal plane of tibiotalar joint and obviate surgery related neurovascular injury [158]. Incorporated with an extramedullary alignment frame, the innovate surgery approach can minimize the amount of bony resection, optimize tibial and talar components positioning and preserve the bone-implant contact area, all of which finally guarantee the survival rate of porous Ta ankle prosthesis [151].

The histological analysis of this porous Ta based ankle prosthesis retrieved from a 50-year old female patient revealed the bone ingrowth percentage in tibial and talar components was more than those retrieved porous Ta hip and knee components [159]. Meanwhile, active bone remodeling was found within the porous Ta layer even 3 years post-surgery. Though regional osteolysis and metal wear debris could not be avoided, both of which did not jeopardize the stability of the prosthesis. Nevertheless, decreased bone density of distal tibia adjacent to the tibial component still presented in this patient, indicating the stress shielding effect and related bone resorption could not thoroughly be eradicated by the use of porous Ta based ankle prosthesis [159].

2.7 Dental implants

Aimed to increase surface energy, extend bone-implant contact area, improve surface hydrophilicity and facilitate mesenchymal cells or osteoblast progenitor cells adherence, surface roughness design of dental implants has now gone virus and has been proved to enhance the progress of osteointegration and angiogenesis [160, 161]. Therefore, the spongy bone like structure of porous Ta can be one explanation for its superior biological and mechanical property to many other metal materials in terms of rapid osseous ingrowth and bone-to-implant contact, both of which directly influence the survival rate of dental implants in the long run [162]. The histological and histomorphometric analysis has validated the osseoincorporation property of porous Ta implants derived from the rapid formation of vascularized bone tissues not only on the surface but also in the inner pores, which further reinforced the interlocking force between the implants and human jaws [163]. The canine model test revealed the porous Ta section could provide a more rapid new bone formation and stronger stability for the porous Ta enhanced titanium implants compared to its conventional screwed titanium counterparts [164].

The porous Ta-enhanced titanium dental implant has now been supposed to be an effective therapeutic method for implanting treatment of certain patients associated with periodontitis [165], alveolar bone defects [166] and even maxillofacial tumors [167, 168]. For the porous Ta segment can provide an expanded three-dimensional space for the infiltration and differentiation of osteoblasts as well as the accumulation of vascular endothelial cells [38, 169]. In addition, this novel implant has also been used in immediate revision surgery for previously failed dental implantation based on the superior osteointegration of porous Ta [170]. The immediate loading tests of porous

Ta enhanced implants demonstrated significantly less marginal bone loss than that of threaded implants (0.43 ± 0.41 mm Vs 0.98 ± 0.67 mm) after 1-year of functional loading [171]. This result was then further corroborated in a retrospective study in which an average of 0.28 mm bone gain could be found in porous Ta enhanced group, but the Ti group showed an average of 0.2 mm marginal bone loss after 1-year of implant loading [172].

However, mechanical flaw of this porous Ta enhanced dental implants may locate at the junction of middle and distal third portion, for the middle portion is produced as slender sharp in order to accommodate porous Ta sleeve and welded to distal apex portion [173]. Accordingly, potential fragile fracture may occur at this facet when the implant is to be inserted in the socket of maxilla or mandible with high bone density. Meanwhile, the unsterile oral cavity where more than 500 kinds of bacteria harbor can be a challenge for the dental application of porous Ta [173]. Therefore, in-depth studies that can enhance the antibacterial property of porous Ta are still needed because the microbial environment of oral cavity and orthopedic sites is obviously different.

3. New development of porous Ta for bone tissue engineering

3.1 Additive manufactured porous Ta

Except for conventional techniques including CVD [30, 174], foam impregnation [175] and powder metallurgy [176], various additive manufacturing methods have been introduced to produce novel porous Ta scaffolds with different pore size and porosity, but comparable mechanical properties with human cortical and trabecular bones [177] (see Table 1). Comparison tests performed with cellular and animal models have revealed similar or even better biological and mechanical performance of printed porous Ta scaffolds than their porous Ti counterparts with the same porosity and pore diameter (see Table 2) [178-182]. Moreover, as a high-end technique, additive manufacturing can help manufacturers to produce porous Ta implants with tailored pore size and porosity to resist different biomechanical loading stress in different parts of the human body. Incorporated with Compute Aided Design (CAD) software, additive manufacturing thus makes personalized porous Ta implants or prostheses for individual patient possible. Several printed porous Ta products have successfully been applied in clinic recently.

Wang et al. [183] have designed and produced a printed porous Ta knee prosthesis for revision surgery for an 83-year old female patient suffered from chronic inflammation and unendurable pain of left knee after a previous total knee arthroplasty (see Figure 2). The X-ray showed severe bone defect in the medial tibial plateau, varus deformity of the left knee and loosening of tibial component, all of which were formidable challenges to be addressed by conventional surgical techniques. With the help of CAD, the authors corrected the anatomic alignment of the left lower limb and fabricated personalized knee prosthesis which can precisely match the bone defect area for the definite revision surgery. Twelve months after the final revision surgery, the patient recovered to normal activity with no more complaints about the affected limb. After that, the same team fabricated personalized porous Ta fibular and femur implant for reconstruction surgery following the same designing and manufacturing process[44].

Table 1: The mechanical properties of osseous tissues and porous Ta produced by different techniques.

Osseous tissues	Manufacturing technique	Porosity (%)	Pore size (μm)	Strut size (μm)	Elastic modulus (GPa)	Compressive strength (MPa)	Yield strength(MPa)	0.2% strength(MPa)	Proof	Ref
Cortical bone		3-5			7-30	100-230				[177]
Trabecular bone		50-90			0.01-3.0	2-12				
	CVD (porous carbon scaffold)	75-85	400-600	40-60	2.5-3.9	42-78				[30]
	CVD (porous SiC scaffold)	70-85	150-400	40-60	10-30	35-100				[174]
	Foam impregnation	65-80	400-600		2.0-4.6	100-170				[175]
	Powder metallurgy		100-400		2.0 \pm 0.3	50.3 \pm 0.5				[176]
		55			1.5 \pm 0.3			100 \pm 10		
	LENS	45			7 \pm 0.6			192 \pm 7		[181]
		27			20 \pm 1.9			746 \pm 27		
	SLM	80	500	150	1.22 \pm 0.07	28.3 \pm 1.2	12.7 \pm 0.6			[182]
		75		540			23.98 \pm 1.72			
	SEBM	80		392			19.48 \pm 1.45			[44]

	85		386			6.78 ± 0.85	
SLM	70	500	400	3.10±0.03			[179]
SLM	80	300-400		2.34±0.2	78.54±9.1		[178]

Notes: CVD, Chemical Vapor Deposition; LENS, Laser Engineered Net Shaping; SLM, Selective Laser Melting; SEBM, Selective Electron Beam Melting.

Table 2: The biological properties of additive manufactured porous Ta scaffolds

Porosity%/Samples	<i>In vitro</i> tests results	<i>In vivo</i> tests results	Ref
80% Ta	Cytotoxicity test (L929 mammalian cells) <ul style="list-style-type: none"> No cytotoxicity 	Histological evaluation (rat femur defect model) <ul style="list-style-type: none"> The bone defect can be bridged by the new bone with the help of printed porous Ta scaffold Torsion test <ul style="list-style-type: none"> Rigid bone-implant connection can be obtained 	[182]

70% Ta Vs 70% Ti

Cell morphologies (hBMSCs)

- Cells' adhesion, proliferation and vitality were similar.

Cell differentiation

- ALP and mineralized nodule staining levels were comparable.

Quantitative RT-PCR Analysis

- Sp7 and OCN genes levels were comparable.

Histological evaluations (rabbit distal femoral defect model)

- Bone ingrowth rate and depth were similar in two groups.
- Ti groups showed a quick-slow-quick new bone formation pattern
- Ta group showed a gradually slow down style of new bone formation.

[179]

Push out test

- The two groups had similar push out force.

80% Ta Vs 80% Ti

Cell morphologies (hBMSCs)

- Ta group showed better cell viability than Ti group.

Cell proliferation

- Ta group was higher than Ti group after 5-7 days.

Cell differentiation

- Ta group had superior ALP levels and calcium nodule numbers.

Quantitative RT-PCR Analysis

- Levels of Runx2, ALP, Col-1, OCN and OPN genes were higher in Ta group.

Histological evaluations and fluorescence labeling (rabbit distal femoral defect model)

- Ta could stimulate new bone formation as early as 4 weeks.

[178]

30% Ta Vs 30% Ti
modified with
TiO₂ nanotubes,
30% Ti and solid Ti

Not mentioned

Histological analysis (rats distal femur model)

- Ta group had the most significant bone formation after 12 weeks.

Push out test

- Four groups had similar bone-implant interlocking strength.

FESEM micrographs

- Ta groups had persistent bone ingrown in the pores at 12 weeks.
- Ti modified with TiO₂ nanotubes groups showed comparable seamless bone-implant interface with Ta groups.
- The other two Ti groups had inferior bone-implant contact.

[180]

Cell morphologies (hFOB CRL-11372)

- Ta groups presented more flattened cell morphologies, filopodia extensions and mineralization than Ti group

27% Ta and 45% Ta
Vs 27% Ti

Cell proliferation

- Cells proliferated rapidly on Ta samples instead of Ti samples.

Not mentioned

[181]

Immunocytochemistry

- Porous Ta facilitated cells' adhesion and differentiation via a porosity depending pattern.

Note: FESEM, field emission scanning electron microscope; hBMSCs, human bone mesenchymal stem cells.

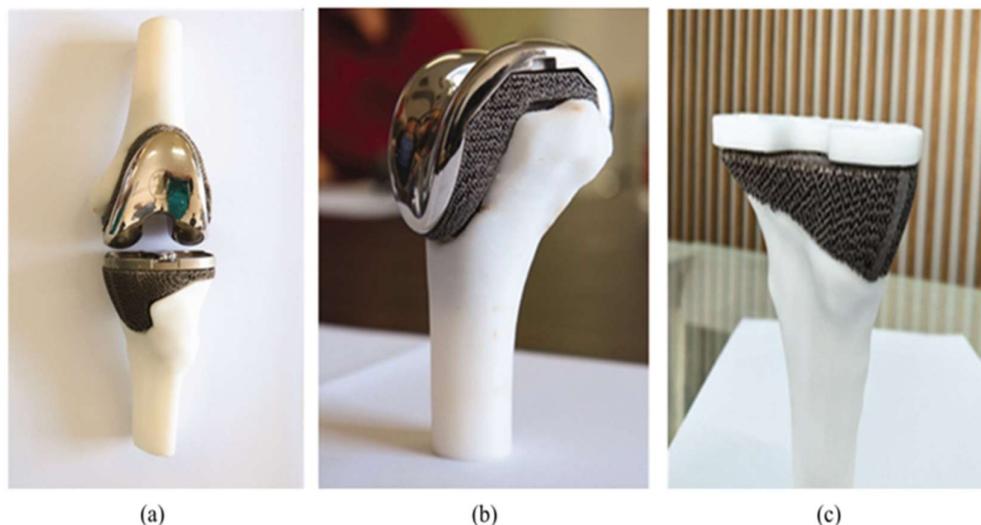


Figure 2: The printed personalized porous Ta knee prosthesis (a), distal femoral component (b) and proximal tibial component (c). Reproduced content is open access [183].

Developmental dysplasia of the hip (DDH) can lead to degenerative osteoarthritis of the hip in adults due to the malposition of acetabulum and femoral head[184]. In order to restore normal acetabular coverage of femoral head and acetabulum index, the additive manufactured porous Ta acetabular patch was introduced in the treatment of 8 adult DDH patients with Crowe I type[185]. Each individualized porous Ta acetabular patch was designed by Mimics 17.0 and 3-matic 9.0 software (Materialise, Belgium) before surgery. Then the loading stress distribution between restored acetabulum by porous Ta patch and femoral head was analyzed by Ansys 17.0 software (Ansys, America). If the stress distribution was uniform, the designed porous Ta acetabular patch would be printed for the final surgery. After an average follow-up of 8.2 months, the VAS scores of 8 patients were drastically decreased (2.92 ± 0.79 before surgery Vs 0.83 ± 0.72 after surgery). Meanwhile, Harris scores (69.67 ± 4.62 before surgery Vs 84.25 ± 4.14 after surgery) and the results of gait analysis were greatly improved after the implantation of porous Ta patch[185].

A printed porous Ta osteosynthesis plate has been used for the treatment of 30-year old male patient with tibial nonunion [186]. The patient had undergone intramedullary nail fixation three times before, but failed to union even associated with iliac crest autograft. Owing to the biological and biomechanical advantages, this novel porous Ta plate (porosity of 80%, elastic modulus of 1.5-10GPa) reunited the tibial shaft fracture uneventfully 5-month post the fourth surgery, and the patient regained normal mobility (see Figure 3).

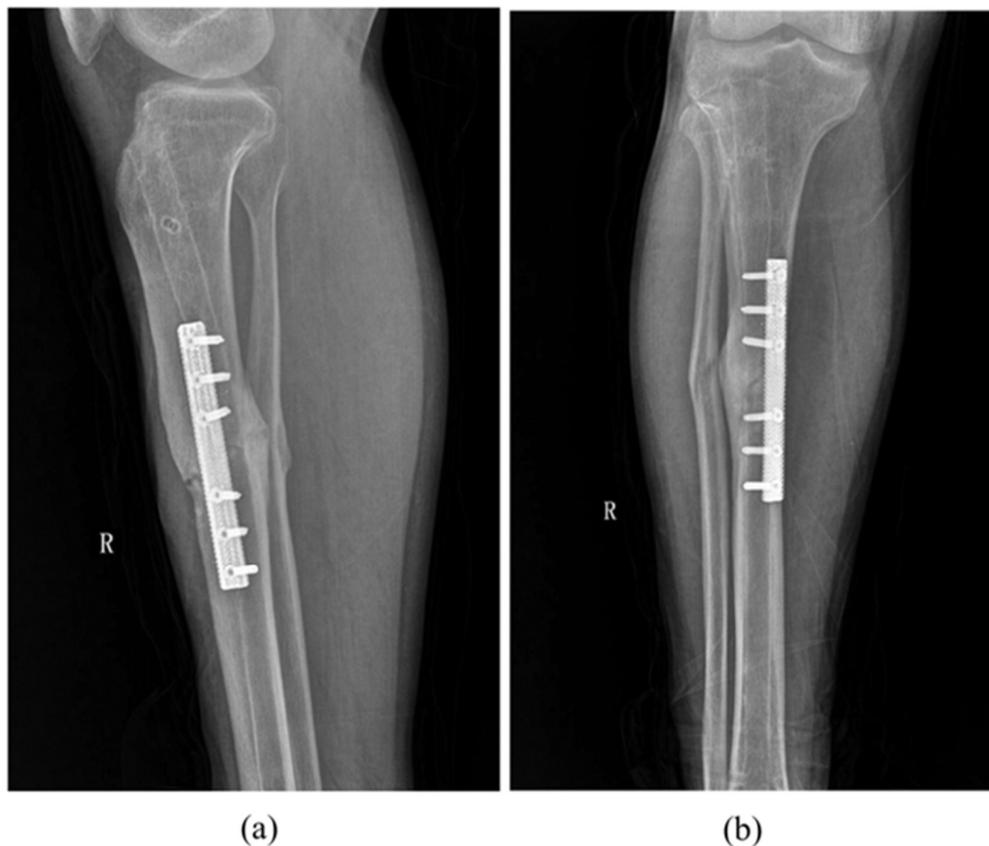


Figure 3: The AP (a) and lateral view (b) of X-ray examination after 5-month follow-up showed fracture healed after the implantation of printed porous Ta osteosynthesis plate. Reproduced content is open access [186].

Nevertheless, the high demand and high price of medically applicable tantalum powder used to produce porous Ta products are the main negative factors that hinder the extensively clinical implementation of novel porous Ta implants or prostheses.

3.2 Surface modification

Actually, the critical drawbacks that may impede further application in bone tissue engineering of porous Ta are the inertness and low level of bioactivity. Therefore, various methods have been introduced to modify porous Ta for further clinical application (see Table 3). These methods can mainly be cataloged into biomaterials coating and surface treatment, all of which are aimed to endow porous Ta based implants or prosthesis with improved osteoconductivity, osteoinductivity and antibacterial property.

Table 3: The biological performance of different methods for Ta modification.

Surface modification	<i>In vitro</i> tests results	<i>In vivo</i> tests results	Ref
ACP nanospheres-PLA coating HA nanorods-PLA coating	<p>Mineralization in SBF</p> <ul style="list-style-type: none"> Abundant mineral deposition could be formed in 1 week. <p>Hydrophilicity</p> <ul style="list-style-type: none"> After soaked in SBF for 1 day, hydrophilicity of the two coating was improved. <p>Protein adsorption and release</p> <ul style="list-style-type: none"> The two nanostructures possessed satisfactory VEGF-FITC adsorption. The amount of BSA release from ACP nanospheres-PLA coating was faster and larger. <p>Cell viability and morphology (MG63 cells)</p> <ul style="list-style-type: none"> The two nano-coatings showed no toxic effects on cells. Cells' adhesion, interconnecting and spreading were better than that cultured on unmodified samples. 	<p>Subchondral bone defect repair</p> <ul style="list-style-type: none"> Significant new bone formation could be found in samples modified by two coatings. By contrast new bone tissues were scanty in the unmodified samples. 	[190]
	CaP nanospheres -PLA coating	<p>Mineralization in SBF</p> <ul style="list-style-type: none"> CaP nanospheres coating transformed into HA nanosheet which could continuously accumulate on the surface of Ta. <p>Hydrophilicity</p> <ul style="list-style-type: none"> CaP nanospheres-PLA coating showed satisfactory hydrophilicity. <p>BSA release</p> <ul style="list-style-type: none"> The transformation from amorphous CaP to HA induced the rapid release of BSA at early stage. <p>Cell viability(MG63 cells)</p> <ul style="list-style-type: none"> Cells established fine adhesion to CaP nanospheres -PLA coating. 	<p>Subchondral bone defect repair</p> <ul style="list-style-type: none"> The modified porous Ta scaffold effectively repaired the defect after 12 weeks.

BMP-7 coating

Not mentioned

Cartilage defect restoration(rabbit model)

- Modified porous Ta significantly facilitated cartilage restoration at 4, 8 and 16 weeks.

Microscopic and histological analyses

- Modified porous Ta groups facilitated calcium salt deposition, as well as formation and maturity of bone and cartilage tissues.

Micro-CT analyses

[196]

- 16 weeks post-surgery, new bone formation could be found around the modified porous Ta
 - The amount of new bone formation was more than unmodified samples.
- Push out tests**
- The modified groups possessed higher maximum push out force.
-

Ta ₂ O ₅ nanotubes films	<p style="text-align: center;">Anticorrosion test</p> <ul style="list-style-type: none"> • Ta₂O₅ nanotube films had excellent biocompatibility, and prevented ions release. <p style="text-align: center;">Contact angle and surface energy</p> <ul style="list-style-type: none"> • Wettability and surface energy of Ta were enhanced by Ta₂O₅ nanotube films. <p style="text-align: center;">Protein adsorption</p> <ul style="list-style-type: none"> • Adsorption of BSA and Fn were significantly more on Ta₂O₅ nanotube films than bare surface, <p style="text-align: center;">Cell adhesion and proliferation (rBMSCs)</p> <ul style="list-style-type: none"> • Adhesion and proliferation of rBMSCs were highly enhanced on Ta₂O₅ nanotube films. <p style="text-align: center;">Osteogenesis-related genes expression</p> <ul style="list-style-type: none"> • Levels of Osterix, ALP, Collagen-I and Osteocalcin were significantly high on the Ta₂O₅ nanotubes films. <p style="text-align: center;">Fluorescence microscopy image</p> <ul style="list-style-type: none"> • Cells cultured on Ta₂O₅ films presented as polygonal morphology and more filopodia than those on bare surface 	Not mentioned	[197]
Nanoporous Ta oxide layers	<p style="text-align: center;">Cell proliferation and morphology (L929 mouse fibroblasts)</p> <ul style="list-style-type: none"> • Nanoporous Ta oxide layers with 25nm pore size greatly enhanced adhesion, proliferation and extension of fibroblasts. 	Not mentioned	[198]
MAO combined with NaOH treatment	<p style="text-align: center;">Mineralization in SBF</p> <ul style="list-style-type: none"> • Substantial mineral deposition can be found on the surface of porous Ta treated with MAO and NaOH etching. <p style="text-align: center;">Cell proliferation (3T3-E1 cells)</p> <ul style="list-style-type: none"> • Cell proliferation on the modified samples was better than the untreated ones at 24, 48 and 72 hours. <p style="text-align: center;">Cell morphology</p> <ul style="list-style-type: none"> • Cells spread over the surface and migrated into the pores of the modified samples, with increasingly filiform protrusions and calcium crystals presented. 	<p style="text-align: center;">Bone ingrowth (rabbit cranial defect model)</p> <ul style="list-style-type: none"> • New bone formation could be found around the modified samples at 4 weeks. • Bone remodeling and neovascularization were also found within the pores. • The cranial defect could be filled by new bone at 12 weeks. 	[201]

PHAs (PHB, PHBV and PHB4HB)-Genta coating	<p>Cytotoxicity and cell adhesion (SaOS-2 cells)</p> <ul style="list-style-type: none"> • PHAs coating showed no toxicity to the cells. <p>Antibacterial properties (<i>S.aureus</i> and <i>E.coli</i>)</p> <ul style="list-style-type: none"> • The concentration of Genta released from PHAs coating effectively inhibited the proliferation of <i>S.aureus</i> and <i>E.coli</i>. 	Not mentioned	[206]
ZnO nanorods–nanoslices hierarchical structure coating	<p>Antibacterial Properties (<i>S. aureus</i> and <i>E. coli</i>)</p> <ul style="list-style-type: none"> • The novel ZnO coating showed a two-stage release pattern and effective antibacterial property. <p>Cytotoxicity (MC3T3-E1 cells)</p> <ul style="list-style-type: none"> • The ZnO nanorods-nanoslices coating had no toxic effect on cells. 	<p>In Vivo Infected Studies (KM mice subcutaneous implantation)</p> <ul style="list-style-type: none"> • The ZnO nanorods-nanoslices coating modified Ta foils had ideal antibacterial performance which could lasted for over 2 weeks <i>in vivo</i>. 	[207]

ACP: amorphous calcium phosphate; HA: hydroxyapatite; PLA: polylactic acid; SBF: simulated body fluid; PHAs: polyhydroxyalkanoates; Genta: gentamicin sulfate; BMP-7: bone morphogenetic protein 7; BSA: bovine serum albumin; Fn: fibronectin; rBMSCs: rabbit bone mesenchymal stem cells; BSA: bovine serum albumin; CaP: calcium phosphate; MAO: micro-arc oxidation; *E. coli*: Escherichia coli; *S. aureus*: Staphylococcus aureus.

Calcium phosphate (CaP) and hydroxyapatite (HA) not only are the mineral components of human bones, but also have been exploited in porous Ta modification for surface modification and drug delivery [187-189]. And the alendronate-CaP coated porous Ta has been verified to fill the bone-implant interface gaps with average length of 0.6mm in rabbit models after 4 weeks [187]. The mechanism behind this successful restoration of simulated bone defects could attribute to the slowly released alendronate, which inhibited the activity of osteoclasts but enhanced that of osteoblasts at the same time. Similarly, the zoledronic acid-HA coated porous Ta rod also gained significantly more bone formation both at peri-implant area and within the inner space compared with the unmodified porous Ta groups in canine models [188]. Zhou et al. introduced amorphous calcium phosphate (ACP) nanospheres and HA nanorods coating to modify porous Ta [190]. When immersed in SBF, the two nanostructures showed rapid mineralization on their surface and the mineral deposition increasingly accumulated within 1 week. Simultaneously, the hydrophilicity of two structures was also significantly improved due to the capillary effects. The ACP nanospheres were observed to transform into HA nanosheets in a rapid pace after soaked in SBF, and this transformation promised rapid mineralization, improved wettability and fast protein release rate [190, 191]. *In vivo*, both the two kinds of modified porous Ta scaffolds repaired the subchondral bone defects with substantial new bone formation, indicating a promising clinical prospect for bone defect restoration.

Bone morphogenetic protein 7 (BMP-7) has been applied in bone and cartilage repairing due to its powerful osteoinductivity since 2001 [192-194]. BMP-7 can act as bone stimulating agent that induces differentiation of mesenchymal stem cells into osteoblasts and chondroblasts [195]. By soaking porous Ta in the solution of BMP-7, Wang et al. [196] coated BMP-7 on the surface of porous Ta rods. Subsequently, the BMP-7 modified porous Ta rods obtained satisfactory results of subchondral bone and cartilage repairing in rabbit models with substantial chondroid-like tissues recovering in the defect areas within 16 weeks. And bone ingrowth depth was found to be 0.2-1.2 mm in the modified samples which finally resulted in rigid bone-implants interlocking.

Fabrication of Ta₂O₅ nanotube layers on the surface by anodization [197, 198] or micro-arc oxidation (MAO) [199] is another approach to ameliorate bioactivity of Ta. With the formation of nanotubes, Ca and P elements containing in electrolyte can be incorporated into the oxide nanotubes by the either aforementioned methods [200]. However, MAO may result in toxic effect on cell viability due to the by-products i.e. reactive oxygen species (ROS) and reactive nitrogen species (RNS). Combined with alkali pretreatment, these toxic elements produced by the process of MAO were dissolved and the newly formed sodium tantalate layer could further facilitate the deposition of apatite in SBF. It is well defined that substantial apatite layer formed on the surface of implants is the prerequisite for bone-implant integration [21, 201]. In this regard, the combination of MAO and alkali treatment will be an effective way to modify porous Ta to boost its osteoconductivity.

Implants-associated infection has long been a thorny problem in clinic, which always results in catastrophic failure and additional expenditure [202, 203]. It is imperative to find rational methods to endow porous Ta with antibacterial property. Polyhydroxyalkanoates (PHAs) are biodegradable and biocompatible materials which can be used as natural carrier for drug delivery and scaffold for tissue replacement [204]. Loading PHAs coating containing antibiotics on the surface of porous Ta and obtaining a controlled antibiotics release will be an optimal choice to avoid implant-associated infection [205]. Rodríguez-Contreras et al. [206] coated PHAs-Genta composite layer both on the outer and inner surface of porous Ta cervical

fusion cages. The continuously released Genta from PHAs coating with homogeneous concentration protected these porous Ta cages from infection of Gram⁺ and Gram⁻ bacteria. On the other hand, a ZnO nanorod-nanoslice hierarchical coating was proposed by Liao et al [207]. *In vitro*, the ZnO nanoslice firstly released from the superficial layer to kill bacteria at early stage and the antibacterial efficacy lasted for 24 hours. By contrast, the release of ZnO nanorod showed a slow but stable pattern. Therefore, the combined ZnO nanorod-nanoslice coating possessed a two-stage release pattern and could last for over 2 weeks *in vivo*, avoiding the implant-associated infection which commonly occurred within 1 week post-surgery [207].

4. Conclusion

With the superior biological and mechanical properties, porous Ta can be an optimal biomaterial for bone tissue engineering, especially when various newly developed methods have been introduced to modify the bioactivity and antibacterial property of porous Ta. And the evolving modification methods will definitely help to expand the scope of clinical application of porous Ta based implants in load bearing parts of human body and endow them with multi-function to cope with various conditions. However, it is necessary to be soberly aware of that porous Ta is not a panacea for all the clinical problems, because patients' conditions are greatly different from each other, it is not a one-size-fit-all approach. Therefore, in order to guarantee the surgical success, surgeons should take each patient's detailed condition (age, gender, BMI, education qualifications, personal financial status, accompanying disease and so on) that may influence the final results into consideration before the operation. Meanwhile, elaborate preoperative planning, meticulous intraoperative management and intensive postoperative follow-up are also critical factors that will definitely determine the success of each operation associated with porous Ta insertion. In any case, additive manufactured porous Ta implants represent the future development in clinical usages especially for individualized treatment, yet abundant randomized controlled clinical trials with sufficient samples and long-term follow-up are still desired to verify their clinical practicability.

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