Journal of Materials Chemistry B

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/materialsB

Current Evidence and Future Directions for Research into the use of Tantalum in Soft Tissue Re-attachment Surgery.

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ABSTRACT

The use of tantalum is well established in orthopaedic surgery. It has a modulus of elasticity that is close to bone and a high yield and ultimate strength allowing it to be used to form large, weight-bearing constructs with a high volumetric porosity conducive to osseointegration. However, its role in soft tissue re-attachment remains undefined due to variable clinical outcomes. Successful re-attachment of tendons to tantalum mega-prostheses, in tumour and revision surgery, has been reported but several authors report almost universal failure of long term soft tissue re-attachment with tantalum patella augments when no residual bone stock is present. It is postulated that these failures are due to a lack of stability of the implants and an inhibitory effect of tantalum on soft tissue integration.

Tantalum has previously been considered an excellent biomaterial for soft tissue integration based on animal studies where implants were retrieved and subjected to mechanical testing. However, clinical studies suggest that this soft tissue in-growth does not reliably tolerate the high mechanical loads that are generated in the clinical setting. Furthermore, recent laboratory evidence suggests that tantalum may in fact directly inhibit fibroblasts, limiting the potential for mature collagen fibrillogenesis.

This review collates the evidence from laboratory, animal and clinical studies to inform and guide future directions in biomaterial research and to drive improved outcomes for soft tissue re-attachment surgery.

INTRODUCTION

Tantalum is a rare transition metal and chemical element (atomic number 73, atomic weight 180.05) with an established history of clinical use in a number of specialties (pacemaker electrodes, foil and mesh for nerve repair, radiopaque markers, dental implants and cranioplasty plates). In orthopaedic surgery it is used in porous form. It is manufactured by vapour deposition onto a carbon foam skeleton. This is designed to give typical porosities of around 80%. The subsequent repeating dodecahedron array of regular interconnecting pores[1,2,3] is similar in arrangement to the appearance of cancellous bone but is more uniform.[4,5]

In its porous form, tantalum has an ultimate strength of 110MPa, a yield-strength of 51MPa and an elastic modulus of 3.9GPa and an excellent strength to weight ratio. This allows large weight-bearing constructs to be formed. The young's modulus is much closer to that of cancellous (6.8GPa) and cortical bone (17GPa) than titanium, cobalt chromium or stainless steel (110GPa, 210GPa and 230GPa

respectively)[6] and as a result there is a reduced risk of stress shielding and surrounding osteopaenia.[4,5]

Tantalum demonstrates excellent osseointegration with integrating bone seen in as little as 8-12 weeks in animal studies.[7] Bone in-growth is facilitated by high initial stability secondary to a high frictional coefficient. A unique surface micro-texture on the metal struts also fosters biologic attachment at the cellular level and interconnecting pores enables supporting small blood vessels to grow through the structure.[5,8]

As an implantable material, tantalum has displayed excellent biocompatibility and safety in the medical and dentistry literature.[8] This is likely due to its chemical stability and corrosion resistance,[7] but also due to its ability to form a self-passivating surface oxide layer (Ta_2O_5) in-vivo. The oxide formed on the surface of tantalum implants has been reported to remain stable over a wide range of pH values.[6]

Although tantalum is well recognised for its excellent osseointegrative properties its role in soft tissue re-attachment is less defined. Multiple metals have been used previously (and are still in use currently) in this role, including stainless steel, titanium alloys and cobalt chromium in numerous solid, mesh or porous designs, through different manufacturing processes and with multiple surface coatings. Although some excellent results have been seen, these materials do have several limiting factors such as low volumetric porosity, high modulus of elasticity and low frictional characteristics.[8]

This review aims to evaluate the published literature and collate data from clinical, animal and laboratory studies in order to define the role and outcomes of tantalum in soft tissue re-attachment surgery and to highlight important areas for future research.

METHOD

Search Strategy

The search term “tantalum” was applied to PubMed, Google Scholar and Cochrane databases, with no limits. The titles and abstracts of 2132 papers were screened for their relevance and those deemed potentially relevant were reviewed in full. 38 articles were identified and included. The search was performed on January 4th, 2015. References cited in the articles identified by the initial search strategy were also reviewed in order to identify any further eligible studies. A total of 50 articles are included for review.

Eligibility Criteria

All animal or human studies evaluating porous tantalum for the attachment of soft tissues were included and reviewed. Laboratory studies investigating the effects of tantalum on cells were also included and reviewed. Relevant data were extracted and considered.

LABORATORY STUDIES

Tantalum has historically been considered biologically inert due to the formation of a passivating surface oxide layer that forms in-vivo. Animal studies have suggested that it does not produce an inflammatory response or stimulate giant cells in surrounding tissues.(3,9-11) However, more recent laboratory studies have demonstrated that tantalum is not inert and has a number of recognised effects on different cell types. A summary is presented in *Table 1*.

Osteoblasts:
Early studies suggested tantalum had no effect on osteoblast behaviour in comparison to plastic or conventional prosthetic metals in tissue culture.(12) However, Ninomiya et al. found that porous tantalum "significantly" increased the proliferation and mineralisation of murine (MC3T3-E1) osteoblasts compared to titanium mesh, cobalt chromium beads and controls after 7 days (specific values are not provided). Furthermore, it was found that cell maturation was delayed, with reduced production of Alkaline Phosphatase and Osteocalcin. These findings are favourable for increased osseointegration leading to an increase in the number of bone forming cells within the implant material.(13)

Another study separated human osteoblasts into those from younger (<45 years old and healthy) and older (>60 years old) patients' bone. Cells were retrieved directly from bone discarded from orthopaedic procedures and cultured on porous tantalum, titanium mesh and culture plastic. This study supported the stimulatory effect of porous tantalum on osteoblasts. Surprisingly, the increase in proliferation of osteoblasts from older patients was much larger (12 times higher than titanium mesh and 16 times higher than culture plastic) than that seen in younger patient cells (4 times higher compared to titanium mesh and 6 times higher compared to culture plastic).**(14)**

Chondrocytes:
Porous tantalum was found to be chondro-conductive in a dynamic environment when cultured with adult canine or emu chondrocytes. Although static cultures had no growth, the dynamic cultures were diffusely covered with cartilaginous matrix that was heavily populated with mesenchymal stem cells resembling chondrocytes. There was glycosaminoglycan staining distributed throughout the matrix and a high type II collagen content.(15)

Leukocytes:
Peripheral blood mononuclear cells (PBMC) and polymorphonuclear neutrophil leukocytes (PMN) were isolated from the blood of 6 healthy volunteers and cultured with porous tantalum or equally sized, non-porous, metallic discs of different materials used in orthopaedics (tantalum, titanium, titanium alloy, stainless steel, tantalum coated stainless steel) for 24 hours. PMNs showed a statistically significant increase in cytokine release in response to the porous tantalum compared to other materials ($p<0.01$) and non-porous tantalum ($p<0.05$). Interleukin (IL)-1ra release was at least four times higher on the porous material (>600pg/ml) than on the metal discs and controls (<150pg/ml). IL-8 release was 6 times (>3000pg/ml) that seen on other materials and controls

(<500pg/ml). The release of IL-8 from these cells was also increased by three times in contact with the non-porous tantalum (>1500pg/ml) compared to other metal discs.

Porous tantalum also caused statistically significant increases in IL-1ra (>2200pg/ml versus <1500pg/ml), IL-6 (>4500pg/ml versus <1000pg/ml) and Tumour necrosis factor-α (>500pg/ml versus <200pg/ml) from PBMCs when compared to cells in contact with the other non-porous metallic discs and controls. The difference in cytokine release between tantalum and porous tantalum conditioned media was statistically significant ($p<0.01$). The release of IL-2 from PBMCs was not elevated suggesting that mainly myeloid leukocytes were activated.

The bactericidal capacity of blood and conditioned media that had been in contact with these metals was also assessed. After 24 hours, the reduction in *Staphylococcus aureus* survival was statistically significant in porous tantalum conditioned medium compared to the media conditioned with other materials and controls. Control medium enabled survival of three times more colony forming units than porous tantalum conditioned medium, and almost twice as many as non-porous tantalum disc conditioned media. This suggests that the bactericidal capacity of whole blood is enhanced in the presence of tantalum and more so if it is in its porous form. It is known that cells can respond to the surface structure and chemistry of implanted material. In this study, leukocyte activation at the surface of porous tantalum induced a microenvironment, which may enhance local host defence mechanisms.(16)

Fibroblasts:
Fibroblasts are responsible for synthesis and deposition of type I collagen and have a key role in soft tissue re-attachment. Maloney et al. has previously shown that fibroblasts can respond directly to metal wear debris. The authors found that cells phagocytosing titanium particles (isolated from membranes obtained during revision arthroplasty) showed morphological change, increased cytoplasm, polarisation of ingested material and increased metabolism with increases in prostaglandin, cytokine and tumour necrosis factor alpha (TNFα) release.(17) Prigent et al. cultured fibroblasts (cell lines L929 and NIH 3T3) on multiple smooth surfaces (copper, titanium, titanium-tantalum alloy and plastic controls) and though cell behaviour was deemed “normal” it was observed that the proliferation, amount of adhesions and cytoplasmic connections were reduced on the metals in comparison to plastic controls. There was no significant difference between the titanium and the titanium-tantalum alloy. (18)

Plenk et al. studied the effect of particulate debris on human dermal fibroblast (established directly from skin biopsies) behaviour. Separate culture media were augmented with multiple material particles of different sizes. Aluminium oxide (particle size <5μm), dental gold, stainless steel, titanium and tantalum (particle sizes 10-50μm). Particles smaller than 10μm (aluminium oxide) were phagocytosed by the cells, larger particles were surrounded by cells but not ingested. Cells laden with particles displayed mitotic activity and their rates of proliferation were reduced.(19) Mostardi et al. studied the concentration

dependent effects of titanium and tantalum debris on fibroblasts retrieved directly from human volunteers. The fibroblasts behaved identically towards titanium and tantalum debris, ingesting debris smaller than 10μm and surrounding larger particles. With all particle sizes, higher concentrations (10-20 particles per cell) proved cytotoxic for both metals. Surprisingly, culture medium that had also been in prior contact with high concentrations of titanium and tantalum particles also caused cell death.(20)

Jordan et al. studied the effect of tantalum on chick tendon fibroblasts in a fibrin gel contraction model. In the control group, cell-mediated contraction resulted in the formation of a ligament like structure between 2 brushite anchors. In the treatment group it was found that the presence of tantalum blocks reduced contraction of the fibrin gel substrate and it was concluded that this demonstrated decreased fibroblast activity and a reduction in the potential for mature collagen fibrillogenesis.(21) Furthermore, light microscopy of the cells revealed a marked difference in cell morphology in those cultured with tantalum compared to controls. The cells were rounded and not attached to the substrate. These findings show a direct effect on cell activity and suggest a significant reduction in the cells' abilities to produce mature collagen.(22)

ANIMAL STUDIES

Multiple animal studies have been performed in a bid to ascertain the ability of porous materials to enable tissue ingrowth and to maximise the variable conditions to improve the potential success of this process. A summary is provided in *Table 2*.

Despite the effects seen on cellular behaviours, Matsuno et al. found no inflammatory response to subcutaneous tantalum wires in canines using light microscopy.(23) Animal studies also attempted to ascertain the soft-tissue in-growth capabilities of porous tantalum, examining the restoration of function, tissue in-growth, strength of attachment and histology of the interface.

In a canine model, Hacking et al. subcutaneously implanted tantalum blocks and mechanically tested the soft tissue interface using 'peel test' in a servo-hydraulic tensile test machine at a rate of 5 mm/min. At 4, 8, and 16 weeks, the attachment strength to porous tantalum was 61, 71, and 89 g/mm respectively. This was three- to six-fold greater than with porous cobalt-chromium beads. The point of failure for the majority of these constructs was within the soft tissue rather than 'pull-out' of the soft tissue and the authors concluded that the soft-tissue reattachment was stronger than the surrounding tissue.(24)

Reach et al. reattached canine supraspinatus tendons between 2 tantalum washers allowing return to normal gait by 3 weeks post-surgery. Despite an initial reduction to 33%, supraspinatus muscle mass recovered to 92% by 12 weeks ($p<0.01$).(25) At this stage 140% of the weight-bearing force was going through the operated limb, potentially due to an increased tendon footprint area or due to the non-operated limb being overused in the recovery period.

Itälä et al. reattached canine patellar tendons between 2 tantalum washers. The bottom washer was cemented to the tibial-tuberosity in a bid to prevent bone-marrow passing through the interconnecting pores to the soft tissue interface. This removed the potential stimulatory effects of bone-derived cells and growth factors (present in bone marrow) from influencing the repair, more closely resembling the likely conditions when reattaching soft-tissues to a tantalum prosthesis (in revision, infection or tumour surgery where large metal constructs are used, without bone or bone-marrow contacting the soft tissue reattachment). Weight-bearing of both hind limbs was measured by guiding the animals to walk freely over a custom force-plate (NK Biotechnology, Minneapolis), measuring the maximum ground reaction force. The mean maximum ground reaction force for 5 runs was calculated for both legs in each animal and expressed in Newtons. Only 1% difference in ground reaction force was seen after 6 weeks. Ex-vivo quadriceps volume of both hind limbs was measured (water displacement method) and had returned to symmetrical readings by 12 weeks. The authors also measured 'force-to-failure' of the tendon insertion by loading the constructs ex-vivo (custom-jig and universal testing machine, MTS Systems Corp, Minneapolis, MN), on average there was a 24% reduction in 'force-to-failure' at 6 and 12 weeks, compared to the non-operated leg.(26)

Histology of retrieved prostheses in animal studies

Hacking et al., reported complete subcutaneous tissue in-growth with neovascularisation in their retrieval study of porous tantalum blocks in a canine model. The organisation and density of the in-grown tissue increased between 4 and 16 weeks and was found to be greatest in the peripheral 2mm of the implant.(24)

Reach et al. found 'Sharpey-like' and collagen fibres inserting onto the surface of the porous tantalum, with alignment of fibres streaming from the metal trabeculae toward the long axis of the tendon. Histo-morphometric analysis showed time-dependent increase in the density of collagen tissue filling the metal voids. The in-grown tissue, however, was inhomogeneous compared with the highly organised structure of mature tendon tissue.(25)

Itälä et al. did not find the association between implantation time and the quantity of fibrous tissue in-growth significant. 42% of the available porous space was occupied by in-grown tissue at 3 weeks, 50% at 6 weeks and 54% at 12 weeks. However, the quality of the tissue in-growth did improve with time, to denser and more organised connective-tissue, more closely resembling mature tendon tissue.(26)

Pore size

The size of the pores within the three-dimensional foam structure has been demonstrated to have a significant effect on tissue in-growth, peel strength, vascularity of in growing tissues and on the frictional coefficient of the material, which is a key factor in initial stability. Tantalum's mechanical advantages allow constructs to be strong enough to allow patients to fully weight-bear after

surgery in some situations even with a high porosity and a large pore size. This is important because higher levels of tissue in-growth occur, with greater vascularity and increased attachment strength, as pore size and porosity increase.[27-29] Taylor and Smith compared the tissue ingrowth capabilities of porous methyl-methacrylate cement implants with pore sizes of 42μm and 360μm in rats. The smaller pore size prevented capillary penetration, although some collagen formation was observed. The larger pores readily supported capillaries and cellular material.[30] Chvapil et al. tested collagen-polymer compound with varying porosity for ingrowth capabilities and suggested that pores in excess of about 100μm are required for penetration of highly vascularised connective tissue. Smaller pores tend to become filled with more avascular tissue as they do not support capillaries.[31]

Hacking et al. found that porous tantalum (pore size 400-600μm) achieved up to 6 times the pull-off strength when compared to a beaded cobalt chromium (pore size 90μm) surface when examining the strength of subcutaneous tissue attachment.[24] A similar study by Bobyn et al. used peel-testing to assess the attachment strength of soft tissue to strips of sintered cobalt alloy of increasing pore size (16, 31 and 90μm mean) on a stainless steel plate. An 'Instron universal test machine' was used at a speed of 0.5cm/min to record a load-displacement curve for each pore size and found that the largest pore size (50-200μm, mean 90μm) produced a mean peel strength of 27.5g/mm at the 16 week point. Smaller pore sizes of 16μm and 31μm (mean) only provided peel strengths of 6.8g/mm and 13.2g/mm respectively at the same time point. Within the first 4 weeks the peel strength provided by the larger pores showed more than a six-fold increase compared to the medium or finest pores (11.4g/mm, 1.5g/mm, 1.0g/mm respectively). Histologically, less penetration of interdigitating fibrous tissue was seen with smaller pore sizes.[28] However, the positive effect of pore size does have an upper limit. Salvatore et al. examined soft tissue response to polyurethane sponges of 6 pore sizes, ranging from 280-3200μm. Histological observation revealed that implants with the 2 smallest pore sizes of 280 and 600μm became rapidly filled by 2 weeks with moderately cellular, moderately vascular tissue and mature collagen. Implants with pore sizes larger than 600μm took as long as 4 weeks to become filled by a less vascular and less cellular tissue in which substantial collagen formation was absent.[32]

Another theoretical disadvantage is that the high percentage of inter-connected pores hypothetically allows transport of wear particles to the host-implant interface, risking lysis and early loosening. Rahbek et al. implanted metal cylinders of porous tantalum (mean pore size 550μm) and glass-bead-blasted titanium (non-porous) into the femoral condyles of canines and polyethylene particles were then injected into the knee joints. The spherical particles consisted of pure crystalline high-density polyethylene with mean diameter of 2.09μm (0.2-11μm) on automatic image analysing equipment, 7% of the particles were less than 1μm diameter. The particles were suspended in sterile hyaluronic acid at a concentration of 1.2×10^9 particles (5mg) per ml. 5mls was injected into each knee weekly for 5 weeks.

A reduction in particles and an increase in bony in-growth were seen in the porous tantalum cylinders compared to the roughened titanium. The authors hypothesised these findings were due to the interconnected pores enabling free movement of fluid through the implant, transmitting joint pressures to the tantalum-bone interface and washing away debris. In the cases using solid titanium cylinders, this effect was prevented and debris settled at the implant-bone interface.(33)

Fixation

Good fixation is dependent on high initial stability of an implant, preventing excessive motion at the host-implant interface. It is presumed this can damage fragile, immature tissues and vessels. Jasty et al. studied the effects of stability on tissue in-growth by implanting porous metal cylinders into canine femurs and subjecting them to varying cyclical loading of 0, 20, 40 or 150μm of oscillatory motion for 8 hours each day for 6 weeks using a specially designed loading apparatus under anaesthesia. Good bony in-growth occurred with 20μm or less micro-motion. At 40μm micro-motion the in-growth consisted of part bone, fibrocartilage and fibrous tissue. Those subjected to 150μm micro-motion were in-grown with dense, heterogeneous, fibrous tissue. Trabecular micro-fractures were seen around the majority of implants subjected to 40μm (3/5 implants) or 150μm (4/5 implants).(34)

Bobyn et al. demonstrated the formation of bursae around smooth tantalum discs inserted into the flanks of canines. They concluded that this was suggestive of excessive motion due to the low coefficient of friction of the relatively smooth, non-porous discs.(28) However, in orthopaedics, tantalum is typically used in its porous form. The rough surface is important in providing a high frictional coefficient and immediate stability.(24)

Recreating the bone-tendon interface

The transition between histological zones of a normal enthesis are essential in reducing the stiffness mismatch between soft-tissue and bone and contribute to the ability of the interface to bear load.(35) In a preliminary study by Inoue et al. (presented at the Orthopaedic Research Society meeting, 1995) attempts were made to recreate this histology in canines, by interposing autogenous, cancellous bone blocks between tendon and tantalum. This study saw resorption of bone grafts and no mechanical advantage was provided over the controls of direct tendon reattachment to the prosthesis. There was also no histological evidence of fibrocartilaginous transitional zones.(36)

In a second study, Inoue et al. augmented this repair with autogenous bone marrow in an attempt to stimulate enthesis formation. It was reported that functional load bearing improved to 90% of the pre-operative level by 16 weeks and that mechanical testing found the tensile strength was 43% of the contralateral side, which was significantly higher than in the direct tendon attachment group (25%), or those with only bone graft (26%). It is of note that none of the failures occurred at the insertion of the tendon into the bone block. Histological evaluation showed some reconstitution of the 4 zones of tendon-

insertion. Tendon fibres with round or oval chondrocyte-like cells were arranged in rows, corresponding to the un-calcified fibrocartilage zone. Between this and the bony foundation, large, round cells were arranged in rows corresponding to the calcified fibrocartilage zone.(37)

In a follow-on study, Higuera et al. examined the potential of recombinant human osteogenic protein (rhOP-1) to act as a bone marrow substitute when augmenting a repair. Cancellous allograft was used in a bid to reduce the operative time and donor site morbidity linked with autografts. At the tendon-bone interface, abundant, organised fibrous-tissue was seen buried into the bone matrix, with aligned collagen fibres. A transitional structure similar to enthesis morphology was described. The bone integrated well with the metal. The samples with more distinguished transitional layers were the strongest on testing, failing at the bone-metal interface. There was however a significant increase in the production of heterotopic bone formation in the rhOP-1 group.(38)

HUMAN STUDIES

The results of human studies are variable despite encouraging results of animal studies discussed above. *Table 3*. Summarises the findings of human studies in this field.

Mega-prostheses in tumour or revision surgery

A 'mega-prosthesis' is any prosthesis designed to replace a portion of, a whole bone or multiple bones after resection for either infection, tumour or revision surgery. They can be extremely large and can include more than one joint (e.g. hip and knee), restoring limb length, function, joint replacement and soft tissue reattachment. Functional soft tissue reattachment of tendons and ligaments to a prosthesis has always proven difficult and multiple strategies have been trialled previously.(Fig 1.) There are no randomised controlled trials (RCTs) reporting the results of porous tantalum for soft tissue re-attachment surgery but there are several encouraging case series.

Chalkin et al. reported a positive clinical outcome for a patient undergoing revision total hip arthroplasty for infection with a revision prosthesis. A small tantalum pad and compression washers on the lateral shoulder of prosthesis (in the position of the greater trochanter) enabled reattachment of the hip abductor muscle tendons. At 2-year follow-up the patient was able to actively abduct the lower limb against gravity suggesting successful tendon reattachment.(39)

In another published abstract by Kwong and Lin, 2 patients undergoing salvage revision hip arthroplasty received proximal femoral allografts. Porous tantalum blocks were cemented into the greater trochanter and the abductors were reattached to the tantalum. At 80-month follow-up, both patients had normal gait and good hip outcome scores (Harris Hip Scores 74-80).(40)

Holt et al reported a case-series of 7 patients requiring lower-limb salvage prostheses for sarcomas of the tibia and femur. Porous tantalum washers and blocks were used to interpose the tendons or ligaments at insertion points. Hip

abductors were reattached directly to porous tantalum in one patient. At final follow up (81 months) gait had returned to normal and the patient could actively abduct against gravity, enabling a return to work as a fitness instructor with no limitations.

Of the 6 mega-prostheses used around the knee (5 distal femur, 1 proximal tibia), 2 underwent collateral ligament reattachment, successfully restoring the coronal plane stability of these knees. One patient experienced severe stiffness of the knee due to excessive soft tissue in-growth into an earlier design of prosthesis (with large porous tantalum sections), and this required revision at 98 months.(41) Newer prosthesis design includes small tantalum pads at specific attachment points in order to try and minimise the risk of stiffness for this reason.

Patella augmentation

The majority of literature published on the topic of human soft tissue integration into porous tantalum focuses on the use of patellar augments in revision total knee arthroplasty (TKA) or reconstruction of the patello-femoral joint. Revision patients have some residual bone stock that is usually strongly attached to the tendon by an intact enthesis. These patients experience high rates of success when augmented with porous tantalum as their success relies on osseointegration. Post-patellectomy patients undergoing surgery to reconstitute their patella have no bone stock remaining and the augment must heal directly to the tendon.

Ries et al. compared the outcomes of these 2 groups with patellar bone loss, receiving a porous tantalum augment sutured onto the extensor mechanism. The revision surgery group had 50% or more bony coverage of the patellar augment (11 patients), whilst the post-patellectomy patients had no remaining patellar bone stock (7 patients). In the group with over 50% bony coverage, one component became infected and loosened (previous two-stage revision TKA for infection), whereas the remaining 10 components remained stable at minimum 12-month follow-up and had good clinical improvement in range of movement (from 7˚-105˚ pre-op to 0.5˚-121˚ post-op) and Knee Society knee scores (57.2 – 87.2), giving a 91% success rate. All 7 patellar components without bone stock loosened and failed within one year. Two of these developed necrosis of the extensor mechanism, requiring multiple subsequent salvage procedures.(42)

Tigani et al. studied a cohort of ten patients undergoing patella augmentation, one patient with no residual bone stock (post-patellectomy) loosened at 17 months and required removal. The other nine implants with residual bone stock integrated well.(43) Jordan et al. revealed similar findings in 5 patients with no residual patellar bone stock. All implants failed to integrate and became loose by 2 years. All patients were symptomatic and all required further surgery. It was of note that the mean time between initial patellectomy and augmentation was 13 years.(22)

Kwong et al. reported varied results in their cohort of 7 post-patellectomy patients. 1 procedure was abandoned intra-operatively due to an inability to close the contracted soft tissues over the tantalum implant, 3 loosened and required removal within 15 months, 3 were well fixed clinically and radiographically at the last follow up (7, 8 and 19 months), despite all patients complaining of on-going pain, stiffness and dissatisfaction (which the authors postulated may represent early loosening). The authors noted the number of prior operations ranged between 3 and 15 and the time between patellectomy and augmentation ranged from 5-21 years. These results were not separated out so the specific effects of these variables cannot be ascertained.(44)

A case report by Nanjayan and Wilton describes a novel technique of fixing the patella augment to bare tendon. A pocket was created in the quadriceps tendon for the porous base to sit in and this was sutured closed. A window was then cut into the tendon and the patellar button was cemented onto the encased augment through this. Clinically, there was significant improvement of pain and stiffness, with good patella tracking at eight-year follow-up, despite initial concerns of on-going symptoms during the first 2 years. It is of note that this patient had rheumatoid arthritis and was of low physical demand.(45)

Infection

Laboratory studies found that tantalum has a potential protective effect against infection,(16) and this was echoed in a clinical study of 144 patients undergoing revision total hip replacement for proven infection. 64 patients received tantalum implants and 80 received titanium implants. A significant ($p=0.006$) difference was seen in the re-infection rates between the groups, with 2 re-infections in the tantalum group (3.1%) and 14 in the titanium group (17.5%). The authors do not give further information regarding whether this was due to the same causative organism (persistent infection) or a new organism (re-infection).(46)

Delamination

Of concern, is one case report of delamination of porous tantalum from its base plate in an uncemented tibial component for total knee arthroplasty. Friction between the tantalum layer and the baseplate may then lead to dissemination of metal debris and symptomatic metallosis.(47)

DISCUSSION

Porous tantalum is already used in orthopaedic surgery but its full potential may not yet be recognised. The evidence for soft tissue integration in animal studies is encouraging as a return to normal function is reported. However, in human studies the results are variable and for certain indications the results are extremely poor.

When the osseointegrative capabilities of tantalum can be capitalised upon, a high rate of success can be expected.(42) Tendons with an intact bone-tendon interface enable dependable osseointegration of the bone-block to tantalum,

preserving the transitional zones of the enthesis, which are essential for attachment strength and dissipating load at the tendon interface.(35)

When a bone block is not retained, the mechanical strength of in-grown fibrous tissue is fairly poor (16-25% of the contralateral limb), despite good functional recovery in some cases.(27,36,37) Studies attempting to recreate the enthesis structure using bone-blocks augmented with autogenous bone marrow or rhOP-1 were successful in improving the transitional histology and the mechanical strength (43% of the contralateral limb).(37,38) More work on this topic seems crucial to improving the efficacy of this material in situations where a high strength of attachment is required.

When comparing animal and human studies, it is important to note the disparity in outcomes between groups. In animal studies, healthy, young candidates with healthy joints and a high regenerative potential are used. Tendons are freshly and sharply dissected off the bone and immediately reattached to the porous tantalum. Joints are supple, flexible, and have a good blood supply at the time of surgery providing favourable conditions for successful tendon re-integration.

In the clinical scenario, the tissues are likely to have reduced potential for healing, as often these are older patients or affected by infection or tumour. As an example, the extensor mechanism of the knee has poor vascularity in the revision scenario, especially when numerous surgeries have been performed through multiple incisions.(42)

Another factor postulated by Jordan et al. to be of significance in the success of soft-tissue reattachment, is the time between patellectomy and the restoration of the patellar thickness. The mean time between patellectomy and augmentation in their cohort was 13 years, allowing soft tissues to contract. Restoring the patella height puts contracted tissues with poor vascularity under tension, compromising the blood supply further and hindering the healing potential.(22)This 'overstuffing' of the patella-femoral joint may be the reason that Kwong et al. encountered an inability to close the soft tissues after implantation in one case, and why Ries et al. report 2 cases of post-operative extensor mechanism necrosis and discontinuity in their cohort.(44,42)

Implanting porous tantalum augments directly onto patellar tendon provides another challenge in the provision of initial stability necessary for in-growth. The patello-femoral joint experiences forces of up to 4 times bodyweight on stairs and up to 7 times bodyweight on squatting, subjecting the interface to a great deal of micro-motion and shear-stresses, preventing soft tissue integration.(48) Poor results can be expected in this scenario unless added stability can be provided by novel fixation,(45) or a method of augmenting or improving the mechanical strength of in-grown tissue is utilised.

When bone graft and intact bone blocks are not appropriate (tumour or infection), improving the quality of in-growing soft tissue is important, making this an essential focus for future study. Tantalum exerts effects at a cellular level and by manipulating these pathways it may be possible to stimulate the cells responsible for controlling direct soft tissue integration.

Excellent rates of osseointegration may be due to a stimulatory effect that is seen on osteoblasts (especially in patients over 60 years old).(14) The stimulatory effects of tantalum on leukocytes up-regulates the bactericidal capacity of whole blood,(16) which may explain the improvement in re-infection rates when compared to titanium for infected revision hip arthroplasty (3.1% versus 17.5% respectively).(46) The chondro-conductivity of tantalum is also encouraging for the development of cartilage-covered metallic constructs.(15)

Phagocytosis of particulate tantalum debris is shown to inhibit fibroblast activity and this effect is cytotoxic at certain concentrations,(19) but this is not necessarily material specific.(20) However, in one study where efforts were made to avoid particulate debris, an inhibitory effect was still seen on the behaviour, proliferation and collagen production of chick tendon fibroblasts. If the presence of solid tantalum does indeed inhibit these cells then the healing potential of soft tissues may be reduced.(22)

The passivating layer forming on the surface of this material in-vivo improves its biocompatibility, but this layer may also play a role in local tissue-healing and cell behaviour. As the thickness of this layer increases, so does the adsorption of proteins (albumin, fibrinogen and gamma globulin). Manipulation of this layer may play a role in altering the bone and fibrous in-growth properties.(6-8,49)

Animal studies established that pore size plays a key role in facilitating in-growth. Pore sizes greater than 100μm allow rapid penetration of vascular tissue, necessary to support the higher cellularity and metabolic demand of soft tissue in-growth.(2,31) Pore sizes up to 600μm allow rapid in-growth of soft tissue, but beyond this a negative effect is seen, in-growth is slower and constitutes less vascular and cellular tissue with poor collagen content.(32)

Stability is also important for organised tissue in-growth.(34) Multiple methods of attaching soft tissues to the porous material are described within the literature and currently available implants provide this attachment in different ways. Initial fixation must be robust enough to prevent the creep characteristic of tendon tissue reducing mechanical fixation over time,(50) but compressing the tendon too firmly, may cause ischaemia. These competing requirements highlight the importance of a rapid, sustainable, biological fixation.

Currently available implants have considered these factors, utilising favourable pore size and robust fixation methods that avoid tissue ischaemia. A further understanding of the specific effects of tantalum on the cells responsible for soft tissue healing is now required. It may then be possible to manipulate the properties of the material or the behaviour of cells by augmenting the construct or altering the local conditions to improve the in-growth potential and attachment strength.

CONCLUSION

Porous tantalum is well recognised for its ability to readily osseointegrate. This quality can be used to facilitate reattachment of a tendon where the bone tendon interface has been preserved using a bone block. When this is not possible we

must provide the stability and conditions favourable for successful integration. It is extremely difficult to provide this environment in post-patellectomy knees to enable integration, and this is reflected in the almost universally poor results of tantalum for this application, rendering its use for this indication questionable. However, there are encouraging clinical reports of functionally successful soft tissue integration of the hip abductors and collateral ligaments of the knee, but as yet no retrieval analyses have been performed to confirm histological re-attachment. In addition, we now know that tantalum is not as inert as previously considered and further work must be done to better understand its effects in an effort to manipulate the pathways and improve reliability, success and strength of soft tissue reattachment directly to this biomaterial.

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Laboratory studies	Cell lines	Study design	Morphology	Outcomes	Conclusion
Ninomiya et al. 2014 (13)	Osteoblasts Murine MC3T3-E1.	Cells cultured on porous tantalum, titanium mesh, cobalt chromium beads	Delayed maturation, reduced production of alkaline phosphatase and osteocalcin	Increased proliferation and mineralisation at 7 days on the porous tantalum compared to other metals and controls.	Porous tantalum is favourable for increased osseointegration.
Sagomonyants et al. 2010 (14)	Human Osteoblasts from bone removed during orthopaedic procedures.	Osteoblasts into 2 groups: young (<45) and older (>60). Cells cultured on tantalum, titanium mesh or culture plastic	Mineralisation higher on Tantalum vs. Titanium mesh at 3 weeks	Tantalum stimulated proliferation compared to titanium mesh x4 (younger) or x6 (older). Tantalum stimulated proliferation compared to plastic x6 (younger) or x12 (older) ($p<0.001$)	Tantalum stimulates cell proliferation and improves bone forming capabilities of human osteoblasts, especially in older patients
Gordon et al. 2005 (15)	Adult emu and canine chondrocytes.	Chondrocytes cultured on small sections of porous tantalum in static and dynamic environments	Type II collagen content in the dynamic canine culture was 84%		Porous Tantalum is chondro-conductive in vitro in a dynamic environment when cultured with emu or canine chondrocytes
Schildhauer et al. 2008 (16)	Peripheral blood mononuclear cells (PBMC) and polymorphonuclear neutrophil leukocytes (PMN) were isolated from the blood of 6 healthy volunteers.	Cells cultured with either porous tantalum, a metallic disc (titanium alloy, titanium, tantalum, stainless steel, tantalum coated stainless steel) or culture plastic (control) for 24 hours		In the presence of porous tantalum; PMNs: Statistically significant ($p<0.01$) increase in the release of IL-1ra (4x) and IL-8 (6x). PBMC: Statistically significant increased ($p<0.01$) release of IL-1ra (1.5x), IL-6 (4x) and TNFα (2x). IL-2 release was not increased. Staphylococcus aureus survival significantly reduced by the presence of porous tantalum in conditioned medium (3x more colony forming units on control culture after 24 hours).	Increased leukocyte activation and increased bactericidal capacity of whole blood was seen in the presence of porous tantalum over controls, other materials and solid tantalum.
Maloney et al. 1996 (17)	Human macrophages.	Cells cultured with titanium particles isolated from membranes obtained during revision surgery	Increased cytoplasm, polarisation of ingested material and increased metabolism with increases in prostaglandin, cytokine and tumour necrosis factor alpha (TNFα) release		Fibroblasts respond directly to the presence of particulate metal debris.
Prigent et al. 1997 (18)	Fibroblasts – L929 and NIH 3T3.	Cells cultured on polished titanium, titanium-tantalum alloy, copper and plastic discs.	Cytoplasmic connections spreading and adherence were reduced on all metals in comparison to plastic.	3T3 fibroblast numbers reduced on titanium (36,000) and titanium-tantalum alloy (44,000) compared to plastic controls (58,000). L929 fibroblast numbers reduced on titanium (46,000) and titanium-tantalum alloy (51,000) compared to plastic controls (70,000).	Fibroblast proliferation, connections and adherence were reduced on all metals in comparison to culture plastic. No significant difference in cellular behavior was seen in the presence of titanium-tantalum alloy compared to pure titanium.
Plenk et al. 1980 (19)	Human dermal skin fibroblasts directly from skin biopsies.	Culture media augmented with particles of aluminium oxide, gold, stainless steel, titanium and tantalum.	Cells heavily laden with particles displayed mitotic activity and reduced proliferation.	Cells phagocytosed smaller particles (aluminium oxide), the cells surrounded larger particles.	Particulate debris reduces proliferation of fibroblasts.
Mostardi et al. 1997 (20)	Fibroblasts retrieved directly from human volunteer blood samples.	Cells cultured with different concentrations of titanium and tantalum particulate debris (1, 2, 10 and 20 particles per cell).	At higher concentrations, fibroblasts were seen to round up, shorten and disappear.		Higher particle concentrations (10-20 particles per cell) proved cytotoxic for both metals. Surprisingly, culture medium that had also been in prior contact with high concentrations of titanium and tantalum particles also caused cell death even

					after removal of all particles.
Jordan et al. 2014 (22)	Chick tendon fibroblasts.	Chick tendon fibroblasts cultured in the presence of porous tantalum blocks (with no particles).	In the presence of porous tantalum, cells were more rounded and less adherent to the substrate	The presence of tantalum reduced contraction of a fibrin gel substrate demonstrating decreased fibroblast activity and a reduction in the potential for mature collagen fibrillogenesis.	Tantalum had a direct effect on cell activity and significantly reduced the cells' abilities to produce mature collagen.

Table 1. – A summary of the findings of laboratory studies discussed in this review.

Animal Studies	Subjects	Study design	Histology	Weight bearing/ Muscle mass	Mechanical testing	Conclusion
Matsuno et al. 2001 (23)	Wistar strain rats (number not given)	Metallic wires (titanium, hafnium, niobium, tantalum and rhenium) implanted into subcutaneous tissue and bone of rats. Removed and assessed after 2 or 4 weeks.	Wires encapsulated with fibrous connective tissue, surrounded by fibroblasts and mesenchymal cells. No inflammatory response. Direct contact of new bone after 2 weeks, remodeling after 4 weeks.			Tantalum was found to have good biocompatibility and osteoconductivity with no inflammatory response.
Hacking et al. 2000. (24)	2 dogs	8 dorsal subcutaneous porous tantalum implants for 4, 8 or 16 weeks.	Complete tissue ingrowth. Vessels visible at interface and within pores. Tissue maturity and vascularity increased with time.		Peel tested in a servo-hydraulic tensile test machine at a rate of 5 mm/min 4 weeks – 61g/mm 8 weeks – 71g/mm 16 weeks – 89g/mm	Tissue attachment to tantalum (pore size 400-600μm) up to 6x stronger than Cobalt chromium porous beads (pore size 90μm). Tissue maturity, vascularity and strength increased with time
Reach et al. 2007 (25)	40 dogs	Supraspinatus tendon reattached between 2 tantalum washers. Assessed at: 0 weeks - 7 dogs 3 weeks - 11 dogs 6 weeks - 11 dogs 12 weeks - 11 dogs	Sharpey-like fibres inserting into metal. Time-dependent increase in collagen fibre density in pores.	Force plate found normal weight bearing by 3 weeks. Muscle volume recovered 92% mass by 12 weeks.	Tendon-implant strength assessed in universal testing machine, compared to contralateral, unoperated limb 0 weeks - 39% 3 weeks - 67% 6 weeks – 99% 12 weeks – 140%	Gait and load bearing returned to normal at 3 weeks. Mechanical strength of the interface reached normal by 9 weeks and exceeded non-operated strength by 12 weeks.
Itälä et al. 2007 (26)	33 dogs	Patella tendon reattached to tibia using porous tantalum washers. Lower washer cemented to prevent bone marrow augmentation. Assessed at: 3 weeks - 11 dogs 6 weeks - 11 dogs 12 weeks – 11 dogs	42-54% of pores filled with fibrous tissue. Volume of tissue ingrowth was not time dependent. Density of tissue was time dependent.	Compared to non-operated leg: Ground reaction force 3 weeks - 76% 6 weeks - 99% 12 weeks - 99% Muscle volume: 3 weeks - 79% 6 weeks - 97% 12 weeks - 103%	Compared to non-operated leg with Universal testing machine: 3 weeks - 33% 6 weeks - 76% 12 weeks - 76%	Ingrown tissue density improved with time. Mechanical strength, ground reaction force and muscle volume also increased with time. Functional strength returned despite maximum mechanical strength only being 76% of contralateral leg.
Bobyn et al. 1982 (28)	12 dogs	24 stainless steel plates with strips of porous cobalt chromium of increasing pore size (16, 31, 90μm) implanted in 12 dogs for 4, 8, 12 or 16 weeks. To ascertain the effect of pore size on attachment strength and histology	In larger pore size, moderately cellular, well collagenised fibroconnective tissue was seen. More organized than that seen in lower pore sizes. Time dependent maturation and increase in collagen content.		Universal testing machine at 4 weeks: 16μm - 11.4g/mm 31μm - 1.5g/mm 90μm - 1.0g/mm 16 weeks: 16μm – 6.8g/mm 31μm – 13.2g/mm 90μm – 27.5g/mm	Increased maturity and mechanical strength of ingrown tissue with increasing implant time and pore size
Rahbek et al. 2005 (33)	8 dogs	Cylinders of porous tantalum and solid titanium implanted into femoral side of knee joint with	A decrease in polyethylene particles was seen surrounding the porous material. Increased bony ingrowth was			Porous tantalum enables circulating fluid, reducing polyethylene wear particles at the

		either perfect fit or peri-implant gap. Polyethylene particles injected into joint weekly for 5 weeks.	seen in the porous material.			implant-host interface.
Jasty et al. 1997 (34)	20 dogs	Porous metal cylinders implanted in canine distal femurs and subjected to varying cyclical load (0, 20, 40, 150μm motion) 8 hours per day for 6 weeks using a specially designed loading apparatus	Bony ingrowth at 20μm or less motion. 40μm motion caused ingrowth of organised bone, fibrocartilage and fibrous tissue. 150μm motion caused ingrowth of dense, heterogenous fibrous tissue surrounded by a bony neo-cortex shell.			Excessive micro-motion (deemed in this study as 150μm) prevents ingrowth of organised tissue such as bone.
Inoue et al. 1995 (36)	Dogs (number not stated)	Supraspinatus tendons reattached using custom porous titanium implant, augmented with cancellous autograft to examine the effects on insertional histology and strength	No histological evidence of fibrocartilaginous transitional zones.		No mechanical advantage over controls (direct tendon attachment).	All bone blocks were absorbed and provided no histological or mechanical benefit.
Inoue et al. 2002 (37)	9 dogs	Supraspinatus tendons reattached using custom porous titanium implant, direct tendon attachment, attachment with intact bone block, cancellous autograft and cancellous autograft augmented with autologous bone marrow to examine the effects on insertional histology and strength.	In the bone marrow group, some clear reconstitution of the four transitional zones of tendon insertion.	In the bone marrow group, load bearing returned to 90% of contralateral side by 16 weeks Supraspinatus muscle volume 85.5% of contralateral side by 16 weeks	Tensile strength of bone marrow augmented reattachment 43% of strength of an intact tendon insertion. Direct tendon reattachment 16%. Cancellous autograft 17%.	Augmenting tendon reattachment with cancellous bone and autologous bone marrow dramatically improves histological and tensile strength
Higuera et al. 2005 (38)	12 dogs Randomised into 2 groups, bone marrow (BM) (6 dogs) or rhOP-1 (OP) (6 dogs).	Supraspinatus tendons reattached using custom porous titanium implant augmented with cancellous bone graft and either bone marrow or rhOP-1 for 15 weeks to examine the effects on insertional histology and strength	Evidence of transitional insertion zones, tissue ingrowth and adhesion. Calcified area around the repair was over 5 times larger in the OP group.	At 15 weeks loadbearing had recovered to 78% (OP) and 81% (BM).	Tensile strength was 24% (OP) and 38% (BM) of the contralateral side.	Histological and mechanical results are comparable in these studies but a high rate of heterotopic ossification was seen with the use of rhOP-1

Table 2. – A summary of the findings of Animal studies discussed in this review

Human studies	Number of patients (prostheses)	Study design	Prosthesis	Diagnosis	Length of follow up (months)	Function/outcome	Complications
Chalkin et al., 2005 [39]	1 (1)	Case report	Proximal femoral endoprosthesis with inset tantalum for abductor attachment	Loss of proximal femur secondary to trauma and infection	24	Harris Hip Score 61	Nil
Kwong and Lin.2010 [40]	2 (2)	Retrospective case series	Porous tantalum sleeve, supplemented with cement	Salvage reconstruction of failed total hip arthroplasty	Mean 76	Mean Harris Hip Score 77	Nil
Holt et al., 2009 [41]	7 (7)	Retrospective case series	Trabecular metal knee endoprosthesis	Post resection of bone tumours (5 osteogenic sarcomas, 1 malignant fibrous histiocytoma, 1 Ewing's sarcoma)	Mean 72	Mean musculoskeletal tumour society functional evaluation score of 29 (95% of normal)	1 revision for stiffness and loosening at 98 months
Ries et al., 2006 [42]	18 (18)	Retrospective double cohort case series	Porous tantalum augmentable patellar implant Group 1 – no residual bone stock Group 2 – greater than 50% bone stock	6 prior patellectomy 6 failed TKA 5 isolated patellar component loosening 1 osteoarthritis with severe patellar bone loss	12	Group 2 – improvement in Knee society knee and function from 57.2 and 64.2 to 87.2 and 78.3.	All Group 1 implants loosened within one year. 9% patients in Group 2 developed loosening after an infection
Tigani et al., 2009 [43]	10 (10)	Retrospective case series	Porous tantalum augmentable patellar implant	Total knee arthoplasties (1 previous patellectomy, 9 deficiency or weakness of patellar bone precluding patellar resurfacing)	45	Knee Society Score improved from 40.8 to 88.8	1 loosening in the patellectomy patient
Jordan et al., 2014 [22]	5 (5)	Retrospective case series	Porous tantalum augmentable patellar implant	Previous patellectomy	24	Mean Oxford Knee Score at one year 32.3	All five implants had loosened and failed by 2 years
Kwong et al., 2008 [44]	7 (7)	Retrospective case series	Porous tantalum augmentable patellar implant	Previous patellectomy – 3 had TKR and 4 had trochlear replacement simultaneously	Mean 13	Mean Oxford Knee score 10.7	43% implants loosened
Nanjayan and Wilton. 2014 [45]	1 (1)	Case report	Patellar implant - trabecular metal shell	Rheumatoid arthritis, previous patellectomy and multiple revision knee arthroplasties	96	Pain free on mobilising, no functional score	Nil
Tokarski et al., 2015 [46]	990 (990)	Retrospective review	Uncemented acetabular components using either titanium or tantalum	Revision total hip arthroplasty (aseptic loosening 47%, instability 12%, wear 12% and others 14%)	Mean 40	Failure lower with tantalum group 4.4% compared to titanium group 9.9% ($p < 0.001$)	Of hips revised for infection, failure due to a subsequent infection lower in tantalum group, 3.1% versus 17.5% ($p = 0.006$)
Bonutti et al., 2013 [47]	1 (1)	Case report	TKA with a cemented femo-ral component and cementless tibial component that used highly porous tantalum	Knee osteoarthritis	28	ROM 5° to 110° Unable to rise unassisted from a chair	Metallosis secondary to delamination of backside of a cementless tibial baseplate.

Table 3. - A summary of the findings of the human studies discussed in this review.

224x160mm (150 x 150 DPI)