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D a n c e R o u n d

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

METALLOSIS: METAL ION RELEASE FROM METAL-ON-METAL JOINT SURFACE REPLACEMENT – CURRENT CONCERNS AND FUTURE PROBLEMS

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Since its innovation, joint replacement surgery has offered relief from the pain and functional limitation of destructive or degenerate joint disease. The search for the ideal material continues over 120 years later. Recently, using metal-on-metal bearings for younger patients has become the trend to avoid excess wear in high demand patients in the hope of reducing the need to revision surgery. Initial evidence suggested these prostheses offered a durable, functional safe joint that was less likely to be revised than the standard metal and polyethylene joint. A body of evidence is growing rapidly to suggest that metal-on-metal joints are associated with local tissue reactions – metallosis – cellular toxicity, increased serum metal ion concentrations, organ deposition of metal ions, higher rather than lower rates of revision surgery and no functional advantage over any other type of joint replacement. We will consider the reasons for metal ion release; the cellular, local tissue and systemic effects of metal ions and the patient risk and presentation. From the evidence reviewed, serious consideration should be given to the future use of metal-on-metal joint bearings and a suggested follow up plan for patients with such joints is identified and reproduced. Biomed Rev 2011; 22: 57-64.

INTRODUCTION

Joint replacement surgery is commonly performed by orthopaedic surgeons for patients with painful, destructive joint disease limiting their function and quality of life. It is little appreciated that joint replacement surgery was first described some 120 years ago. The Romanian born German surgical pioneer, Thermistocles Gluck (1853-1942) antedated the famous 20th Century pioneers such as Harboush (1), Wiltse (2) and Charnley (3) by more than 50 years. He was ahead of Küntsher (4) by some 50 years with the concept of intramedullary fracture fixation. His interest in bone defects was encouraged by his work in the Balkans as a wartime surgeon between 1877 and 1885. In his 1891 Treatise, Gluck, describes

his observation of a rudimentary external fixator. This was made by a mechanic, and used on a femoral fracture, due to a gunshot in Bulgaria in 1885-1886 (5). Gluck sought to determine suitable material to replace diseased joints with. He describes implants made of aluminium, wood, glass, celluloid and nickel plated steel as being cheap and allowing healing without reaction. However, his favourite material was ivory. He described his experiments with cement "in particular the almost instantaneously congealing stone filler" which can be used as a filler or to provide security to his ivory implants. Even in 1891, with his excitement of pioneering a surgical advance Gluck urged caution. He foretold that wear and tear on the artificial joint could not be anticipated and loss of joint movements and ivory strength could result (5).

Wear of prosthetic joints remains a problem today. As we have passed through the 20th and into the 21st Century, joint replacements have evolved and become more common. Younger patients who expect higher levels of function and, naturally, have long life expectancies are being considered for hip surgery. A good functional result has been achieved based on the innovations of Sir John Charnley using polyethylene lined cups and metal femoral heads. However, high demand produces high levels of wear on the polyethylene cup liners and the potential need for revision surgery.

To withstand wear and provide a durable functional prosthetic joint metal-on-metal joints have evolved and procedures such as hip resurfacing offer a durable, functional, pain free joint whilst avoiding total hip replacement in the younger patient. Alternatively, total hip arthroplasty using metal components with a large femoral head to cup size ratio can be offered to the younger patient. Some studies show good functional results are achieved (6). Rates of wear with metal-on-metal prostheses have been shown to be 20-100 times lower than metal on polyethylene (7) and revision rates specifically due to loosening or femoral fracture are low over a 5 year period (2-3.6%) (8,9). These studies provide an argument in favour of the use of metal-on-metal bearings but evidence to the contrary may outweigh this.

The choice of metal implanted into the human body is governed by several factors. It must resist corrosion in the hostile environment of human tissue. It must be durable for its purpose. It must be inert or bio-compatible. It must be compatible with other components implanted with it. Metal alloys have been found to be most suitable. Stainless steel is the least corrosion resistant of the currently used metals and is used more for temporary purposes. Titanium and cobalt-chromium alloys do not corrode in the body however metal ions can diffuse out of the metals and into the body (10).

In this review we will consider the problem of metal ion release from implanted material; consider what, if any, risk it may pose for patients, and consider whether there is sufficient advantage of metal-on-metal bearings to justify any risks.

WEAR OF PROSTHETIC JOINTS

The articular surfaces of prosthetic joints are subjected to repetitive motion as part of their normal function. During their manufacture, joint surfaces are highly polished to ensure a smooth gliding surface. Any micro-imperfections may be eroded after implantation by localised friction, especially if the joint surfaces are not well lubricated by synovial fluid.

Correct placement of the joint components is vital, the geometry of the prosthetic joint place will influence its function and stability. It has been shown that a steeply inclined acetabular component or a small femoral head size can lead to an abnormal pattern of "edge loading." Edge loading is associated with increased rates of localised wear and in the case of metal-on-metal joints, higher serum metal ion concentrations (11-14). Small femoral head size is also associated with impingement of the femoral neck on the edge of the acetabular cup, resulting in restricted movement of the joint and, again, edge loading and excessive wear of the components (14).

Titanium alloy (Ti-6Al-4V) has been found to be susceptible to abrasive wear and it has been seen that one year after implantation the articular surfaces become covered in a "scratch and gouge" pattern. This is especially seen if any loosening of the components occurs, allowing loose acrylic debris from cement or wear debris from a polyethylene acetabulum liner to interpose between the articular surfaces. This pattern of damage is associated with localised release of metal (15,16).

Coupling of the components used in joint replacement is usually relatively straight forward – manufacturers provide both components as part of a set and the components are compatible with each other. Should any mis-pairing result then the outcome depends upon the metals involved. A reported case exists of an incompatible paring of cobalt-chromium and stainless steel leading to severe wear, local metal deposition and serum metal ion concentrations increased by a factor of 20 (17). Cases of excessive wear are in the minority, a 10 year

follow up study of 100 metal-on-metal hip arthoplasties has found survivorship rates for the femoral component of 98% and the acetabular component 96% at 10 years, that is not requiring revision surgery (18).

CELLULAR EFFECTS OF METALS

Chromium is a trace element, present in the human body. In its hexavelent form (Chromuim VI) it is readily absorbed by the lungs, skin and mucous membranes and is toxic. Cobalt is also a trace element and forms an integral part of vitamin B12. The effects of metal particles upon cell culture have been studied *in vitro*. Cell cultures have been exposed to cobalt and chromium separately and as an alloy. Particles have been generated to be representative of those seen with wear upon a prosthetic joint. It has been seen that nano-particles of cobalt-chrome alloy are more toxic to fibroblast culture that micron sized particles. Nano-particles were more readily absorbed into fibroblasts. They break down readily and form an electron dense cloud within the cell, inducing aneuploidy and cytotoxicity. The effects were greater than those seen with larger micron sized particles (19). Cytotoxic effects upon fibroblasts have also been seen to be greater with metals containing a high cobalt concentration (20) and fibroblast viability can be reduced by up to 95% with concentrations of clinically relevant sized particles of 50 micromoles per cell (21). Following exposure to cobalt, fibroblasts show morphological changes when examined under the microscope. Nucleoli become darker staining, cytoplasmic processes are withdrawn and chromatin condenses irreversibly (pyknosis). Within the cell culture, following exposure to cobalt a significant rise in lactate dehydrogenase is seen, suggestive of cellular injury (22).

When osteoblasts are exposed to cobalt or titanium particles, the secretion of interleukin 8 (IL-8/CXCL8) and monocyte chemotactic protein-1 [MCP-1/ chemokine (C-C motif) ligand 2 (CCL2)] is induced rapidly due to up-regulation of the corresponding chemokine genes. The effect of chemokine secretion is to induce macrophages and neutrophils to migrate to the area. Osteoblast synthetic function is reduced in the presence of cobalt ions, as seen by reduced alkaline phosphatise activity and calcium deposition. The production of type I collagen, the predominant form in bone, is inhibited and the production of osteocalcin, a unique and abundant calcium binding bone protein is inhibited by colbalt. Chromium also inhibits osteoblast alkaline phosphatase (23,24). Macrophages attracted to

the area by the osteoblast secretions absorb metal particles and secrete IL-1β, IL-8 and tumor necrosis factor-alpha (TNF-α), in a particle dependant manner. These cytokines have been shown to have a bone resorbing effect (25). In particular, high levels of IL-1 producing cells have been found at the bone-implant interface during revision surgery for implant loosening. The role of TNF-α in bone resorption and implant loosening has lead to its consideration as a therapeutic target in those who present with aseptic implant loosening (26). Along with IL-1β producing macrophages, CD4+ T cells, helper T cells, are seen to be present in similar number but in excess of CD8+ T cells (27). The effect of metal debris T cell viability and function show some variability in the literature. Unlike fibroblasts viability has not been seen to be affected by metal debris in some *in vitro* studies, but proliferation has been seen to be inhibited by cobalt chromium molybedenum alloys, an effect not seen with titanium alloys (28). An opposite conclusion was reached by Hallab *et al* (29) who found *in vitro* that both Co-Cr-Mo and Ti alloys incubated with serum solutions led to a lymphocyte proliferative response, greatest when the metals formed metal-protein complexes. To add to this controversy, Akbar Brewer and Grant (30) found that at "clinically relevant" concentrations Cr^{6+} ions significantly decreased cell viability, proliferation and activation while increasing apoptosis. Co^{2+} also resulted in a decrease proliferation and cytokine response but no apoptosis.

LOCAL EFFECT OF METALS

At the local tissue level the effects of failing metal-on-metal bearings are well described. A frequent finding is blackening or grey staining of the tissues adjacent to the implant. These findings are described around the hip (31,32) the knee (33-35), the shoulder (36) and the spine (37).

Soft tissue masses in the vicinity of metal-on-metal bearings are not infrequently described. These masses histologically, have been found to consist of macrophages, metal particles, lymphocytes, fibrin and necrotic tissue (31,38). Microscopic examination of macrophages found in these pseudo-tumours has shown them to be laden with black metallic particles (39). Lymphocytes within pseudo-tumours and surrounding tissues may be found diffusely spread throughout or concentrated in the peri-vascular areas. It has been seen that with higher grades of diffuse inflammation around a failing metal-on-metal bearing is associated with an increasing extent of metal particles

in the tissue (40). As with inflammation from other causes, metallosis can lead to involvement of regional lymph nodes. Chromium containing histiocytes have been demonstrated in the enlarged pelvic lymph nodes of a patient 8 years after hip arthroplasty (41).

The size of pseudo-tumours is variable, in some the tumour mass itself is the reason for presentation (42) or in others the effect of the mass on nearby structures giving rise to symptoms may trigger presentation (43,44).

As we have already seen, the effect of metals upon macrophages and lymphocytes includes the secretion of bone resorbing cytokines at the implant-bone interface. This can lead to loosening of the implant and loss of optimum implant position (45-48), erosion of both trabecular and cortical bone (38,47,49,50) and trabecular micro-fractures of varying ages (51).

SYSTEMIC EFFECTS OF METALS

Metals released into the local tissues are absorbed into the blood stream. These metal ions are measurable in the serum and it has been seen that patients with metal-on-metal joint replacements have raised levels of cobalt and chromium in the blood and the urine (52). Blood levels can be several times the normal level but well within the limits of levels identified as toxic in metal industry workers. Metal ions are removed by the kidney and eliminated from the body in the urine (53). Chromium III ions have been seen, *in vitro* when mixed with human serum, to complex with albumin, transferin and immunoglobulins. The complexes formed were then more readily absorbed by macrophages than uncomplexed metal ions (54).

Titanium ions are released from implants slowly and despite being associated with local tissue metallosis, systemic diffusion levels are low. In sheep, following spinal fixation, in has been seen that at 24 months post surgery little systemic diffusion has taken place, at 36 months, titanium ions were present in all tissues (55). Human post mortem studies also demonstrate widespread distribution of metal ions throughout the tissues. Within lymph nodes evidence of fibrosis and necrosis associated with metal laden macrophages has been seen. The presence of metal containing macrophages within the liver and spleen has been shown and although the amounts of metal are higher than is seen in the lymph nodes, dilution in these larger organs makes the overall metal concentration less. Up to ten years after arthroplasty, no evidence of necrosis

or fibrosis was seen in the liver or spleen (56). The alteration of T cell function and viability discussed previously when combined with lymph node fibrosis and necrosis could lead to local immune dysfunction. Small increases, compared to control subjects, have been seen in levels of metal ions found in the frontal cortex of patients with worn metal on metal prostheses (56). The effects of cobalt and chromium ions on nervous tissue described include 1 case of reversible poly-neuropathy with histological evidence of axonopathy (57). Two cases of femoral nerve neuropathy due to a pseudo-tumour mass with histological evidence of complete nerve destruction are also reported (58). Consideration has been given to metal ions released following arthroplasty as potential carcinogens. In has been postulated that chronic stimulation and alteration of lymphocyte function could lead to an increased risk of lymphoma or leukaemia (56,59).

It has been seen that concentrations of metal ions is higher in patients whose prosthesis is worn or is loose. This leads to the question, could serum levels of metal ions be used to identify worn, failing or loose prostheses? It has been suggested that measurement of serum metal ions can be a useful adjunct to assessing metal-on-metal joints and a study has shown a good correlation between high levels of serum metal and wear on the joint surfaces (60). This may prove to be a sensitive indicator of wear if regular measurements are taken. The Medicines and Healthcare Products Regulatory Agency (MHRA) have recommended that patients with serum cobalt or chromium ion concentrations greater than 7μg/L should be further investigated. It was seen that 7 μg/L concentration of either ion, had a 90% specificity but only a 50% sensitivity for hip prosthesis failure (61).

HOW COMMON ARE PROBLEMS DUE TO METALOSIS?

The true incidence of metallosis is unknown as early pathology can be asymptomatic, diagnosis may be difficult, and reporting inaccurate (62). In 2011, the National Joint Registry for England and Wales reported that all cause revision rates at seven years for primary hip replacements regardless of implant type were 4.7% (of a total of 285,600 primary operations) however, metal-on-metal bearings had all causes revision rates of 11.8% for resurfacing and 13.6% for replacement joints (63). It can be seen therefore, that revision rates, within seven years of surgery, for metal-on-metal bearings are higher than revision rates in general, despite the previously quoted evidence of a

lower revision rate when looking specifically at revisions for loosening or fracture (8,9). The vast majority of joints have not needed revision during this time, but this is not to say that asymptomatic pathology has not developed.

HOW DO PATIENTS PRESENT?

Initial symptoms may be vague and patients may present with groin, buttock or lateral hip discomfort. They may present with the sensation of a lump around the hip which may or may not be visible. Sensations of "clicking," "clunking," instability or dislocation are less common and may follow a period of discomfort. The mean time of presentation has been seen to be 17 months post primary surgery in one study (64). Rarely, patients may present with serious local symptoms such as nerve compression or vessel damage (43,44,65).

The natural course of metallosis appears to be progressive once symptoms are present and revision surgery for deteriorating symptoms becomes necessary (66).

CONCLUSIONS AND FUTURE CONSIDERATIONS

At present we do not know how many patients will go on to develop symptoms following their metal on metal joint replacements or resurfacings, we may find that after several more years patients who had been initially asymptomatic run into difficulties. Long term effects of cobalt or chromium deposits in the liver are not well known. Although at 10 years, no necrosis or fibrosis has been seen in livers containing macrophages laden with cobalt or chromium (56) it is not known if this will be the case at 20 or more years. It has been suggested that there may be a link between metal-on-metal bearings and leukaemias or lymphomas (56,59) however, no definitive evidence has, to date, been described.

Revision surgery performed for metallosis is more difficult due to local tissue destruction and is associated with worse outcomes and more complications than revision surgery for other reasons including peri-prosthetic fractures (65,66).

Do the benefits of metal on metal bearings justify the potential complications and risks? Recent meta-analysis shows that functional outcomes following metal-on-metal joint replacements compared to metal on polyethylene or ceramic-on-ceramic joints offer no advantage but potentially metal-on-metal bearings have a higher revision rate (67).

What about those patients who, with the best intentions, have been given a metal-on-metal bearing? What should be done for them? The MHRA (68) and British Orthopaedic Association have issued guidance summarised by Fary *et al* (66) and shown in box 1.

When looking at general revision rates for metal-on-metal bearings rather than rates specifically for loosening or fractures we see that revision rates are higher than for traditional metal on polyethylene joints and, as discussed the surgery is more difficult with a higher incidence of complications and poorer functional results. Potential disadvantages are described at the cellular, tissue and systemic level. Taken with the unanswered questions on long term metal toxicity for a joint which is offering no functional advantage over any other currently used prosthesis we must seriously ask ourselves: should we be continuing to use metal on metal joint prostheses in our patients?

Box 1: *Follow up of post metal on metal joint implants*

- Annual follow up for at least 5 years and more frequently if symptomatic
- Investigate any painful metal on metal joint. Measure serum cobalt and chromium, image the joint with MRI or ultrasound
- If there are concerns about component position or patients in cohorts with higher than expected failure then measure serum metals and image with MRI or ultrasound
- If serum metal ions are greater than 7μg/L then repeat at 3 months and image.
- If imaging shows soft tissue reaction, fluid collections or tissue masses then consider revision surgery.

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