Implant-derived Metals and Health

Focus on Metals from Metal-on-Metal Hip Prostheses

Metal alloy implants and prosthesis devices have been used extensively in medicine to restore joint function and mobility, and markedly improve the quality of life by eliminating bone-on-bone pain. However, local and systemic toxic effects may be associated with release of metals from some implants. The medically-induced issue warrants serious consideration since it is well established that a variety of toxic elements can have additive or even synergistic toxic effects, and we are all subjected to at least low-level chronic exposure to xenobiotic elements from the environment. This review will highlight the potential local and systemic clinical consequences that may result from persistent release and bioaccumulation of specific metals from implants and address the current recommendations for assessing the levels of the metals in patients. Rational for possible clinical interventions to mitigate toxic effects of the persistently released metals will also be discussed.

Titanium (Ti) has been long considered to be an inert biocompatible metal and has been used extensively for dental implants, vascular stints, and orthopedically as plates, screws, wires and in-bone stems for hip and knee prosthesis devices. The “Ti” used may be pure, or alloys that contain variable percentages of vanadium, aluminum and even nickel. Some patients develop immediate or delayed hypersensitivity reactions to the Ti alloy implants. Corrosion is another potential concern especially with dental implants when dissimilar metals (mercury, nickel) are in the mouth and galvanic currents are created. There is sparse research regarding local and systemic toxic effects of Ti dental implants in part due to the difficulty of accurately measuring Ti levels (polyatomic interferents). Potential adverse effects of Ti alloys will be further discussed with respect to metal-on-metal total hip arthroplasty, but it is clear that Ti ion release by electro-corrosion is far less a concern in comparison to metal-on-metal wear or fracture. Titanium levels can be assessed accurately in serum, blood or plasma by some commercial laboratories. Normal serum/blood Ti levels in the absence of Ti implants are typically reported to be < 1 ng/ml. Ceramic and zirconium dental implants may now be used to avoid Ti alloy corrosion issues.

Metal-on-metal Total Hip Arthroplasty

It is well established that circulating levels of specific metals are increased to some extent indefinitely following metal-on-metal total hip arthroplasty (MoM THA) or MoM resurfacing. Unlike the local inflammatory necrotic damage to peri-prosthetic bone and soft tissue, the long-term systemic responses to elevated levels of the specific metals is somewhat controversial and not as well defined. However, due to the short and long term complications associated with MoM THA procedures that have been performed for decades, MoM prosthetic devices are now rarely used. Concern is heightened by the fact that the procedures have been performed on younger and more active patients which raises questions of potential reproductive effects; it has been reported that metal concentrations in blood from neonates whose mothers had metal implants were higher than those of controls.
Total hip arthroplasty (THA) is one of the most successful treatments for patients with severe rheumatism and osteoarthritis, and most THA devices remain functionally intact for upwards of 20 plus years. THA can be a positive life changer or a major calamity. Development of durable and safe prosthetic implant materials is an ongoing formidable challenge. Until very recently the vast majority of prostheses consisted of pairings of alloys of cobalt (Co), chromium (Cr), and molybdenum (Mo) for the acetabular cup and femoral head (Co:Cr:Mo about 60:30:7). The femoral head is attached to a femoral stem/shaft that is composed of Ti alloy; vanadium is a minor component of some Ti alloy stems. The MoM prosthesis bearing surfaces perpetually wear and release Co and Cr\(_3\). Rates of wear are dependent upon device design, surgical technique, level of physical activity and other factors that affect the health of peri-prosthetic bone and soft tissue. Controversy exists concerning the role of electrocorrosion of the metals, including the more resistant Ti alloys, but it is apparent that physical wear is by far the biggest factor in release and sequestration of Co and Cr\(_3\).

From the orthopedic perspective the primary concern is failure of the prostheses due to periprosthetic tissue reactions to the metals. The CAM practitioner is also very concerned about remote tissue deposition and potential systemic toxic effects of the incompatible metal nanoparticles. All patients with MoM THA will have elevated levels of Co and Cr\(_3\) (Ti to a lesser extent) in blood, peri-prosthetic soft tissue and bone, and remote tissues in the body up to 20 years post-operatively (longest reported follow up to date). Local tissue metallosis, also referred to as aseptic lymphocytic vasculitis-associated lesions, can cause pseudotumors, decreased viability of osteoblastic bone marrow cells, osteoclastic bone resorption (release of lead), necrosis, and infiltration of macrophages, eosinophilic granulocytes and lymphocytes. Such metallosis is “silent” and may result in loosening/misalignment of the components that in turn further increases wear and release of metals. Unfortunately, the local tissue destruction is often irreparable and many patients have poor outcomes after required revision procedures. It has been reported that the incidence of symptomatic peri-prosthetic tissue damage is low during the first seven years after MoM THA, higher with specific devices, and more common among females less than forty years of age. Longer term follow up studies are warranted since the release of metals persists indefinitely. It has been emphasized that elevated circulating levels of Co and Cr\(_3\) alone in the absence of corroborating symptoms do not independently predict prosthesis failure.

It is not possible to assess prostheses wear and metal release radiographically, so the levels of metals in serum or blood have been suggested for use as part of the evaluation of the functional condition of prosthetic implants and decisions regarding revision surgery. However, there is limited published data on appropriate reference ranges for the metals which raises question regarding the clinical utility of the data for that purpose.

CAM doctors are also very much concerned about potential systemic or remote tissue toxic effects of the released metal debris. Transition metals such as Co, Cr, Ti, Mo, nickel, manganese and iron induce production of highly reactive oxygen species (ROS) by Fenton or Fenton-like reactions in fluids in the body. Excessive ROS compromise redox buffering and can diminish levels of glutathione. The extremely reactive hydroxy radical is of particular concern because it may cause oxidative damage to proteins, lipids and nuclear and mitochondrial DNA and RNA. Clinical studies have linked MoM THA to white blood cell DNA and chromosomal damage. However, despite theoretical concerns epidemiological studies to date have not found increased risk or incidence of cancer associated with the elevated levels of implant metals in MoM THA patients. Continued surveillance has been suggested as the average follow up was eleven years and the latency for some cancers is 20-40 years. Also consider that hip resurfacing and THA is more common now in younger patients than in the past.

Nonetheless excessive exposure to such metals can result in excessive oxidative stress, inflammation, low levels of quintessential glutathione, and compromised redox capacity. Further, excessive Co has been shown to compromise hepatic cytochrome P450 activity in laboratory rats (Phase I detoxification). It should be noted that it appears that little if any highly genotoxic hexavalent Cr (Cr\(_6\)) is released from the CoCr alloy prostheses.
The most abundantly released metal from the CoCrMo alloys is Co. Cobalt and Cr particles/ions accumulating in lymph nodes can cause necrosis and fibrosis, and associated inflammation is primarily an immunological response. Research regarding systemic toxic effects associated with MoM-THA is rather sparse. However, a 2018 paper from the Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom) reported that the most common issues in MoM THA patients with high levels of metal ions include neurological; hearing and visual impairment and loss, peripheral neuropathy, cognitive impairment, cardiovascular; cardiomyopathy/heart failure, breathlessness, and endocrine; hypothyroidism, malaise, depression. The MHRA states that said conditions usually resolve after revision surgery. There are also case reports regarding neurotoxicity and cardiomyopathy associated with the disseminated metal ions, particularly Co. Possible toxic effects include somatic mutations (animal models), aberrant immune function, impaired renal function, compromised endogenous detoxification (Phases I and II), excessive inflammation, and breakdown of arterial endothelial cell tight junctions. Safe blood levels of Co ions have not been established and Co poisoning is defined by serum Co levels ≥ 5 ng/ml. Is one not to be concerned about potential systemic toxic effects when serum/blood Co levels are 4-10 ng/ml just because a prosthetic implant is thereby implied to be in "good condition"?

Adverse reactions to Co ion release can be clinically silent yet severe, so early detection is very important. The American Academy of Orthopedic Surgeons has recommended assessment of circulating levels of Co and Cr for all MoM THA patients annually (asymptomatic), and every four-six months with mild symptoms. Regulatory authorities worldwide recommend regular follow-up of patients with MoM THA to identify and treat adverse reactions to the metal ions.

Titanium levels will likely be elevated to some extent in patients with MoM THA even when only the femoral shaft is composed of Ti alloy; plasma Ti levels may also be somewhat elevated in patients with Ti alloy plates and rods, and dental implants for crowns and bridges. Titanium has been long regarded as a very biocompatible metal due to its corrosion resistance. However, recent studies have shown that Ti and vanadium (a minor component of Ti alloys) from non-bearing implant components can be released with potential consequential effects both locally and systemically. Specifically, Ti may have adverse effects in blood, fibrotic tissues and osteogenic cells. That Ti corrosion occurs in bone in the absence of wear was demonstrated in a well-designed long-term study in which a Ti wire was implanted into the femurs of rats. The corrosion-released Ti increased blood Ti levels, leading to an increased concentration of Ti primarily in the spleen and lungs and to a lesser extent in the heart, kidneys and liver. There is a dearth of clinical data regarding potential adverse health effects of elevated levels of blood Ti, which is disconcerting since it has been reported that circulating levels of Ti can be 18 times greater 10 years post-surgery than at baseline (Ti alloy acetabular sockets and Ti femoral stems.)

Vanadium (V), an element that interferes with a vast array of biochemical reactions, is another metal that is released from some MoM THA prostheses. Vanadium is a minor constituent of titanium-aluminum-vanadium alloys used that primarily constitute the femoral stem and less frequently in bearing surfaces (acetabular sockets). Serum V levels are expected to be higher than normal (< 1ng/ml) with such Ti-alloy prostheses in good condition (1-2 ng/ml), and even higher with significant prosthesis wear (>5 ng/ml). A case report indicated V toxicity associated with a broken Ti alloy femoral stem and a serum V level of 5.8 ng/ml. The patient exhibited sensory-motor axonal neuropathy and bilateral sensorineural hearing loss.

Clinical Intervention

The most fundamental rule of toxicology is to eliminate the exposure(s). Revision surgery with non-MoM prosthetic materials goes a long way in that regard, but what about the metal ions retained in tissues? Patients that do not have revisions have perpetual exposure to the offending metals. So what might be done on an ongoing basis for asymptomatic patients who still bear functional MoM THA prostheses?
Aminothiols

Aminothiols such as N-AC and GSH enhance Co excretion and decrease tissue Co levels following acute Co intoxication in animal models. Various aminothiols administered in different forms orally or intravenously have been compared in animals exposed to a single dose of Co\textsuperscript{60}. After five daily doses, intravenous GSH and oral liposomal GSH were most effective at enhancing Co\textsuperscript{60} excretion; 64% and 47%, respectively. Poorly bioavailable powdered oral GSH was without effect. In patients, the beneficial effects of N-AC to enhance Co excretion have been reported. Of particular interest was the efficacy of very high-dose oral N-AC (300 mg/kg) for ten days to markedly lower blood Co and Cr (up to 87%), and enhance urinary Co excretion. That data from the patients who did not undergo revision surgery are very encouraging, but it would seem to make more sense to use an aminothiol at a reasonable daily dose.

Chelation

It has been recommended that chelation therapy should be reserved for patients who cannot undergo revision. A strong case could be made for consideration of chelation after revision. In a case of severe arthroprosthetic cobaltism, chelation with DMPS after revision eventually resolved all symptoms except deafness (caveat- no control). Chelation with EDTA has also been suggested as a treatment option post-revision, and in animal models of cobaltism EDTA has been shown to be the most effective chelator. Chelation therapy might be given serious consideration for managing the perpetual release of Co, Cr and Ti, and associated pro-oxidative effects. Selection of a chelating agent, timing of administration and clinical efficiency are subjects of debate. Currently there are no established indications for chelation therapy for asymptomatic MoM THA patients. There are case reports regarding chelation with Ca-Na\textsubscript{2}-EDTA or DMPS for asymptomatic MoM THA patients, but that application has not been appropriately evaluated. EDTA has good affinities for Co, Cr\textsuperscript{3+} and Ti, and intravenous EDTA enhances free Cr\textsuperscript{3+} excretion in human subjects; EDTA also decreased oxidative stress and damage to DNA. Without revision using more inert / biocompatible prosthetic materials, the source of exposure is still present and metal levels would no doubt rebound over time after chelation.

Clinical research regarding chelation after MoM THA is long overdue. Intravenous EDTA appears to be the agent of choice, and there is no evidence that chelation will adversely affect the integrity of the prostheses, increase the rate of release of the metals from the devices, or cause undesirable redistribution of the metals. It is proposed that a protocol incorporating dietary/supplemental anti-oxidants and metal conjugating agents (e.g. liposomal GSH, N-AC), and intermittent chelation may greatly ameliorate the potential local and systemic toxic effects associated with the life-long release of metals in patients with MoM THA prosthetic devices.

References


Sarmiento-Gonzalez A et al. Titanium levels in the organs and blood of rats with a titanium implant, in absence of wear, as determined by double-focusing ICP-MS. Ana Bioanal Chem. 2009;393:335-343.


Maines MD et al. Cobalt induction of hepatic heme oxygenase; with evidence that cytochrome P-450 is not essential for this enzyme. *PNAS* 1974;71:4293-4297.


Matharu GS et al. Follow up for patients with metal-on-metal hip replacements: are the new MHRA recommendations justified? BMJ 2018;360:k566 DOI:10.1136/bmj.k566


