Back in Focus: Biologic Reactions to Wear Debris and Corrosion Products

It is my pleasure to introduce this special issue of CeraNews, which is dedicated to the latest clinically relevant findings about particle release from orthopedic implants. This is a time-honored topic! Since the invention of THA by Charnley, there has been clinical concern about the potential for a biologic reaction to implant debris. After the introduction of modularity in the 1970s, there has also been increasing concern about fretting and corrosion products from the interfaces of modular components. The worry about wear and corrosion reignited after the recall of the ASR metal-on-metal hip in 2010. As a result, there has been an explosion of interest in biologic reactions to metal release in the recent literature. However, there is still much to be done. This special issue of CeraNews highlights three frontier topics in clinical research for wear debris and corrosion products, including: genetic susceptibility of tissue reactions to wear debris and corrosion products; metal release in TKA; and potential systemic complications for cobalt release. Finally, although much of the focus has been on adverse tissue reactions from cobalt-chromium alloy, some implications are emerging from wear and corrosion research for ceramic components as well.

FDA: Immunological response of metal containing implants under scrutiny

The US FDA calls for a common engagement involving surgeons, scientists, patients and industry to collect evidence on implant materials. The goal is to develop a better understanding of materials science and the adverse biological responses induced by some materials considered to be biocompatible and though eliciting exaggerated reactions on some patients.

ANSM: Cardiac function to be monitored in patients with metallic heads

The deposition of cobalt species in retrieved heart tissues from arthroplasty patients has been suggested to be associated with heart failures. These findings have been recently confirmed in an epidemiological study published by the French health authorities (ANSM). The ANSM recommends to monitor regularly the cardiac function in patients with metallic bearings.

BIOLOX® delta ceramics failed to stimulate immunological responses

With the increasing use of composite ceramic bearings in THA, a group of researchers led by Joanne Tipper investigated the biological impact of BIOLOX® delta particles. The ceramic particles failed to stimulate an inflammatory response, and did not cause any DNA damage or oxidative stress in human cells in clinically-relevant doses.
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Genetic Susceptibility to Wear and Corrosion Products

Although wear and corrosion are common with orthopedic implants used in millions of patients each year, relatively few patients develop clinically significant adverse local tissue reactions, such as pseudotumors [1], which is suggestive of an underlying genetic susceptibility. What is clear is that currently the reasons underlying a patient’s specific response to metal ions and corrosion products are not yet possible to predict using a generally accepted diagnostic test. Two independent systematic reviews have identified biomarkers that may be utilized as diagnosing ALTR in this setting [1, 2]. Sumner and colleagues’ systematic review [2] found that the most studied markers were tumor necrosis factor-a and interleukin-1β. Genetic susceptibility to innate foreign body responses to excess polyethylene debris has been well recognized, although susceptibility appears to result from a combination of a multitude of genetic polymorphisms [3]. Recently, Kilb and colleagues [4] has identified an “at-risk” genotype in patients for developing pseudotumors around metal-on-metal THAs, which likely would include an adaptive, metal hypersensitivity type immune response. This small case-control study with 26 MOM patients provides clinical evidence supporting the hypothesis of a genetic association with developing a specific type of ALTR. Certain periprosthetic tissue responses, including lymphocyte infiltration and aseptic lymphocytic vasculitis-associated lesions (ALVAL), which can be more severe in those with lower wear and blood metal levels, suggest that a genetic predisposition to metal hypersensitivity may also exist [5, 6]. Taken together, it is clear that a better understanding of the pre-emptive diagnosis of metal hypersensitivity and susceptibility to ALTRs is under development for orthopaedic surgeons to potentially avoid these serious complications for their patients in the future.
Back in Focus: Biologic Reactions to Wear Debris and Corrosion Products (continued)

Metal Release in TKA
Most of the research on metal reactions of wear debris and corrosion products has been completed for THA patients, but comparatively little is known about metal release and their consequences in other total joints, such as TKA. Previous retrieval studies have reported that in vivo metallic debris release mechanisms for TKA may include bearing surface wear (including third-body wear), mechanically-assisted corrosion at the cement-implant interface, and mechanically-assisted taper corrosion in modular junctions [7]. Arnholt and colleagues have recently found metallosis and elevated Co, Cr, and Ti concentrations in periprosthetic tissue from necropsy retrieved TKA [8]. Since these patients died with their TKAs intact, this study adds to the current understanding of metal concentrations in clinically successful TKAs. As research continues to focus on metal reactions in the hip, it will continue to be important to understand the impact of metal release in other joints, like the knee, where CoCr alloys are the dominant bearing surface against polyethylene.

Potential Systemic Complications for Metal Release
Just as research on the local effects of wear and corrosion products continues, both in the hip and knee, so too does research into the potential for systemic effects of metal release from medical implants. The FDA has recently issued a statement and paper about the Agency’s continued efforts to evaluate the safety of implantable metallic medical devices, based upon information learned from devices including metal-on-metal https://www.fda.gov/news-events/press-announcements/statement-continued-efforts-evaluate-materials-medical-devices-address-potential-safety-questions and https://www.fda.gov/media/131150/download. The FDA recently convened an advisory panel meeting to discuss the concerns about immune responses to metal in medical devices in certain patients that might result in exaggerated immune or inflammatory reactions, including those resulting in systemic effects.
Implications for Ceramics?

Of interest to readers of Ceranews is how the increased scrutiny of adverse reactions to wear and corrosion products with metal components is being translated to ceramic implants. For example, when ceramic-on-polyethylene has been used as a control group to compare with MOM hips in the literature, periprosthetic fluid collections have also been observed [9]. However, the fluid collections around ceramic components are generally asymptomatic, except when there is a secondary source of metal release, such as from a modular neck [10]. There are also case reports in the literature of a pseudotumor after fracture of a ceramic component, when the revision involves the use of a CoCr head that articulates with residual ceramic fragments and abrades the metal [11].

Retrieval analyses have demonstrated that the use of a ceramic head is associated with 90% reduction in metal release compared with the use of CoCr head [12]. However, these findings were based on heads and stems that were from the same manufacturer (no “mixing and matching”) and none of the heads in the retrieval study were associated with an ALTR. It is clear, as well, that fretting at the head taper interface is increased when the taper is suboptimally assembled [13]. Thus, to minimize fretting, corrosion, and metal release with a ceramic head, proper assembly under clean and dry conditions is still recommended.


A biocompatible material

- Is able to perform its desired function with respect to a medical therapy.
- Generates the most appropriate beneficial cellular or tissue response.
- Elicits no undesirable local or systemic effects in the recipient.

Two types of cellular or tissue response mechanisms

- Implant surface (bulk)-induced immune reactions that occur immediately upon implantation
- Delayed wear debris-induced reactions that often arise years after the primary surgical procedure and which are induced by wear particles.

Appropriate cellular or tissue response

Appropriate and adequate immune response with a proper activation of the immune cells takes place, including a directed biological response, a good host-implant integration, a desired healing process as well as in the case of wear-induced immune reaction the possible encapsulation of wear particles and their removal.

Dahms K et al. Cobalt intoxication diagnosed with the help of Dr House. Lancet. 2014 Feb 8;383(9916):574. doi: 10.1016/S0140-6736(14)60037-4
Inappropriate cellular or tissue response (continued)

An implant material can activate and initiate an inappropriate immune response. For example, degradation and corrosion of the implant over time can trigger an elevated and uncontrolled immune response with a chronic activation of immune cells and fibrosis that can lead to implant failure.

**Local and systemic toxicity**

Metal ions that are eluted into the peri-implant space or generated by wear and corrosion at the modular junction can either accumulate locally within cells and tissues which surround the implant. However these metal ions can also spread systemically via their transportation through the blood stream and hence can accumulate in distant organs (e.g. liver, heart, spleen ...) that can lead to metal intoxication, which can cause long-term systemic complications to the organism.


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Particle induced cardiotoxicity

An association between THA metal bearings and cardiotoxicity has been observed by several groups. In their investigations, Wyles et al. (2017) and Swiatkowska et al. (2018) found out that heart failures were associated with exposure of metal ions and raised concerns about the toxicity of metal bearings.

Associations between cobalt depositions in the cardiac tissue and cardiac fibrosis and cardiomegaly were demonstrated by Wyles et al. They found a moderate correlation between cardiac cobalt levels and cumulative implant years. Moreover, higher cobalt levels were measured in patients that underwent revision surgery or in patients that had a hip replacement combined with a total knee or shoulder replacement. The authors suggest an association between the accumulation of metal toxins generated by CoCr implant components in a distant organ and systemic long-term complications on the patients. This research work can serve as the basis for further studies investigating the safety of CoCr components used in orthopaedic clinical practice.

Wear and corrosion at the modular junction

Local toxicity – adjacent to implant
Transportation of debris and ions, e.g. via blood
Systemic toxicity – in distant parts of body / distant organs


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Particle induced cardiotoxicity (continued)

Before, Swiatkotwska et al. found that potentially harmful metal species may disseminate into human organs of arthroplasty patients with metal bearings. The authors discovered through histological and elemental analyses an accumulation of wear debris and corrosion products in distant organs (i.e. heart, liver, spleen, etc.) collected post mortem from patients with metal-on-polyethylene hip implants.

The authors exploited a systematic approach employing optical microscopy, laser ablation inductively coupled plasma mass spectrometry, micro-X-ray fluorescence and micro-X-ray absorption spectroscopy. The combination of these methods allowed to assess the distribution and chemical nature of implant debris found in organ tissue samples.

The major finding of the study was that carcinogenic forms of chromium might arise in vital organs of THA patients. The hexavalent oxidation state of chromium (Cr\textsuperscript{VI}) is the most harmful state, however it is very unlikely that Cr\textsuperscript{VI} species originate directly from the implant. Instead, the re-oxidation of trivalent chromium (Cr\textsuperscript{III}) released by metal bearings to carcinogenic Cr\textsuperscript{VI} species may be possible. Under pathological, but also normal conditions cells may generate oxidants. It follows that the oxidation of trivalent chromium to its carcinogenic valence state may be promoted by elevated levels of biological oxidants in the blood.

The presence of cobalt in tissues from MoP patients resulted to be only mildly elevated, although several patients showed cardiomegaly or severe interstitial fibrosis.

Interestingly, titanium oxide was also found within the tissue samples, nevertheless it could have originated from other external sources as it is commonly used in food and personal care products, as well as being present in ambient air.

These findings with limited evidence were confirmed recently by a large epidemiological study performed by Lassalle et al. (2018). The analysis of the French Health Authorities ANSM database (255,350 hip patients) revealed a higher risk for heart failure and cardiomyopathy in patients with metal bearings compared to patients with ceramic bearings. A further increased risk has been identified for women and older patients (≥ 75 years).

The authors recommend to monitor regularly the cardiac function in patients with metallic bearings.


Biological impact of BIOLOX® \textit{delta}

Generating clinically-relevant ceramic particulate wear debris in vitro is a technically challenging process due to the inherent low wear rates of modern ceramics for TJA.

So far, the size, morphology and biological responses of modern composite ceramic for arthroplasty were not investigated. This was made possible by developing innovative wear particle generation, isolation and characterization methods.

Joanne Tipper and her group at the Leeds University investigated the characteristics and biological activity of powder particles and clinically-relevant wear particles, both from BIOLOX®\textit{delta} zirconia toughened alumina ceramics. The clinically-relevant BIOLOX®\textit{delta} wear particles were produced in a hip simulator under extremely severe edge loading conditions. The biological impact of the ceramic particles was assessed using human blood cells from healthy persons. No cytotoxic effects were observed at clinically relevant concentrations. Further the BIOLOX®\textit{delta} particles failed to stimulate an inflammatory response in terms of TNF-\alpha release and did not cause any significant DNA damage or oxidative stress at clinically relevant concentrations.

Very high doses of particles may stimulate the biological responses. But this is very unlikely to be achieved in the real setting due to the extremely high wear and scratch resistance of BIOLOX®\textit{delta}. These findings allowed the researchers to conclude that BIOLOX®\textit{delta} particles have a low biological impact, which may enhance long-term clinical performance.

The wear particles were assessed in terms of:

- Cytotoxicity
- Inflammation
- Genotoxicity
- Oxidative stress

The experimental approaches demonstrated that BIOLOX®delta powder particles do not cause enhanced release of immune-mediators (such as TNF-α) in contrast to CoCr particles (fig. 1).

In contrast to CoCr particles, BIOLOX®delta powder particles do not exhibit genotoxic effects, thus do not cause any DNA damage, again highlighting the excellent biocompatibility and the inertness of ceramics even in its particulate form (fig. 2).