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Mini Review

Metallosis Die Hard

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Abstract

Metallosis is an aseptic fibrosis, local necrosis, inflammation, or loosening of an implant device secondary to metallic corrosion and release of wear debris. The condition has been highlighted recent years due to the clinical complications caused by metal-on-metal (MoM) hip replacement. Although some major types of MoM hip prostheses have been recalled from the market, metallosis is far from over as not only there are still a million implanted MoM hip prosthetic cases worldwide, but also it has been found in non-MoM hip prostheses and other metal implants. This mini review aims to provide recent findings of implants related metallosisin skeletal tissue.

Introduction

Over the past few decades, metals and their alloys have been widely used as implantable materials in orthopedic surgery, in particular hip replacement [1,2]. Among hip prostheses, metal-on-metal hip replacements (MoMHR), which consist of a metal ball and a metal cup forming the bearing surfaces, have been increasingly used over the last two decades. At a time before 2010, 10% of more than 60,000 primary hip replacements annually in the UK, and one-third of 250,000 hip replacements annually in the United States, were MoMHR [2].

MoMHR can lead to shedding of Co/Cr nanoparticles [3], result in pseudotumour and related clinical complications. On 22 April 2010, the Medicines and Healthcare products Regulatory Agency in the UK announced a Medical Device Alert for all MoMHR (MDA/2010/033) due to adverse tissue reaction and clinical complications [4].

The DepuyASR XL and hip resurfacing devices were recalled in August of 2010. In November 2013, it was reported to settle most of the ASR lawsuits for $4 billion which is followed by a second round of settlements for $420 million in March 2015. It is believed that metal wear particles at the bearing surface and metal sleeves between neck and head of hip prosthesis caused local tissue responses and toxic effect.

It was assumed that the problem would be over after the recall. However, Stryker Corp. recalled two of its hip implant systems - the Rejuvenate Modular and ABG II Modular-Neck Hip Stems - in the U.S. in 2012.Since these two types of prostheses do not use MoM bearing, it signified that non-metal-on-metal hip replacement is not exempted from metal toxic effect. It is believed that corrosion and "fretting," which allows minute shards of its metallic components to leach into a patient's tissues, bones and bloodstream.

There are more than one million MoM hip implants, either THA or HRA have been implanted worldwide with large heads implanted in the majority of these patients. The impact on public health and on the health care costs are already considerable and will grow substantially in the next decade, considering the large number of patients implanted and the follow-up needed for lifespan of the implants and also after implant revision to monitor for adverse long-term effects.

Metallosis is also observed in other type of metal implants such as metal rods or plates after implantation so to understand the mechanism is still relevant to clinical orthopaedics.

This mini review aims to provide recent findings of implant related metal toxicity, or metallosis, in skeletal tissue. The terminology, recent clinical evidences, new research development, potential mechanism and future perspective are discussed.

Terminology

Metallosis is defined as aseptic fibrosis, local necrosis, or loosening of a device secondary to metallic corrosion and release of wear debris [5]. It can be related to many different types of metal implants, such as titanium [5,6], cobalt/chromium[6-8] or different joint replacements such as hip, knee and shoulder[6,9-12].

There are other terminology related to metallosis, in particular those caused by MoM hip arthroplasty, such as Adverse Reactions to Metal Debris (ARMD) [13-15] or Adverse Local Tissue Reactions (ALTR) [1,16-18]. ARMD is a collective description of the histopathology observed in association with MoM hip arthroplasties including Aseptic Lymphocytic Vasculitis Associated Lesion (ALVAL), lymphoid neogenesis, granulomatous inflammation and metallosis [13]. ALTRs

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Table 1: Morphology and composition of nanoparticles from three types of hip prostheses.

	MoM HRA		MoM LHTHA			MoM DMNTHA
	(1)	(2)	(1)	(2)	(3)	(4)
Morphology	Circular, irregular	small needle-like	Circular, irregular	small needle-like	large needle-like, large irregular	Circular nanoparticles and large agglomerations
Composition	Cr	Co, Cr, Mo	Cr	Co, Cr, Mo	Ti, V	Co, Cr, Mo, Ti, V

are caused by an inflammatory response to small metal debris particles created by MoM implants [18]. This inflammatory response can lead to metallosis, formation of a bursal soft tissue growth known as a pseudotumor, and generalized synovitis and tissue damage.

In ARMD or ALTR, metallosis are an important part of the clinical complication and pathological processes. However, there are significant variations in clinical manifestation from asymptomatic to severe complications which makes the condition a great complexity.

Recent Clinical Evidences

Typical metallosis is the appearance of wear metal debris in tissue, normally demonstrated as black or yellowished stain of soft or bone tissue [19-21]. Metal particles may be detected by pathological examination [22,23]. However, in many cases the metal particles may not be able to detect by visible black stain, nor by pathological examination.

Histopathological examination demonstrates periprosthetic adverse reactions which is characterized by a pseudo-capsular and neo-synovial mass (pseudotumor) containing a macrophagic infiltrate filled with cytoplasmic inclusions of wear products of uncertain composition [2]. A dense perivascular lymphocytic infiltrate and a variable amount of soft tissue necrosis [23] to a more complex picture defined as ALTR or ARMD, exhibiting a variety of histological patterns [24-26].

These reactions can subsequently lead to muscle, capsule, and soft tissue degradation, as well as tendinopathy around the hip joint. This constellation of events is thought to be the origin of pain, instability, and dysfunction in MoM hip arthroplasties with ALTR.

It was suggested that there was a hypersensitivity type IV reaction to wear debris produced at the MoM interfaces, since the lymphocytic component associated with the presence of a layer of soft tissue necrosis of variable thickness is characteristic of this type of reaction [24,25]. However, metal hypersensitivity is unlikely to explain many of these cases, as the occurrence of ALTR is much higher than its incidence in the general population. High ratio of failure only happens in some type of prostheses, although the compositions of the metal components are very similar to other type of prostheses; therefore, there may be differences of the wear/corrosion metal products in different materials/configurations of the prostheses used.

The unintended consequence of this generation of implants was the occurrence of severe adverse inflammatory reactions of the periprosthetic soft tissues due to the generation of corrosion and conventional metallic wear debris [23]. In particular, increased rates of early periprosthetic soft tissue reactions reported across a diverse spectrum of implant configurations due to the increased risk of corrosion and wear [26-30]; These failures can result in extensive tissue necrosis, injury to abductor muscles and tendons, increased revision complications, and significant patient morbidity [28,31-33].

There are a large variety of clinical manifestations of these conditions; however, metal compositions are identified. The pathological process can be classified as macrophage dominated phagocytosis/cell apoptosis [23], or macrophage/lymphocyte infiltration reaction/tissue necrosis [34,35]. The latter also descripted similar to metal supersensitive type IV [35]. There are overlaps between these pathological processes, and it is very difficult to distinguish the differences in many cases. The key component that activates lymphocytes and adaptive immune responses in this process is still mainly unknown.

New Research Development

Ricciardi [36] and Xia [2] have reported recently on the analysis of periprosthetic tissue and corrosion/conventional metallic wear particles from 285 revision operations which provide comprehensive new evidences to hip arthroplasty related metallosis and clinical complications.

Hip prostheses associated with ALTR can be divided into three major classes of configurations, metal-on-metal hip resurfacing arthroplasty (MoM HRA), large head total hip replacement (MoM LHTHA) and non-metal-on-metal dual modular neck total hip replacement (Non-MoM DMNTHA) (Figure 1). There are distinct differences of the nanoparticles produced between the three configurations [2]. The particles produced can be classified as (1) sliding tribocorrosion (Figure 1A and 1B); (2) edge loading (Figure 1A and 1B) from MoM bearing surface; (3) fretting and crevice corrosion and possibly abrasion at the metallic stem and metallic adapter sleeve interface from MoM LHTHA (Fig 1B); and (4) fretting and crevice corrosion at the neck/stem interface (Figure 1C) from themetallic dual modular neck (Non-MoM DMNTHA).

The morphology and composition of these particles are shown in Table 1. More details can refer to Xia (2016) [2]. More importantly these differences correlate with the histological features of severity

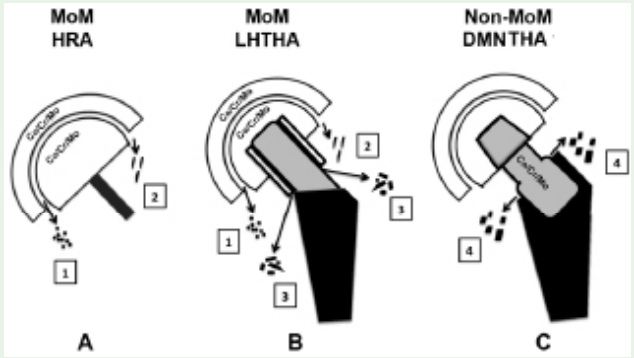

Figure 1: Three common types of configuration of hip prostheses associated with metallosis.

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of ALTR and variability in implant performance [36]. Thus it signifies that the design of hip prostheses plays an important role in the performance of implants, and evidences could lead to the development of effective strategies to prevent or limit the occurrence of adverse event of hip replacement.

In principle, wear metal nanoparticles should be a risk factor to all cells in tissue; however, from analysis of retrieved tissue, majority of wear particles are engulfed by macrophages or foreign body giant cells. Lymphocyte infiltration is secondary to macrophage reaction, and no evidence to show direct uptake of nanoparticles by lymphocytes and fibroblasts. As metal debris are inorganic, there is a missing link that how metal debris can cause lymphocyte infiltration and severe immune/allergic and inflammatory responses.

Potential Mechanism

The potential toxicity of metal nanoparticles could be due to either the particles themselves, or the ions released due to particle corrosion.

Metal debris or particles are foreign bodies to the host immune system. As an important type of innate immune cells and phagocytes, macrophages are the dominant infiltrating cells that respond rapidly to biomaterial implantation in soft and hard tissues [37]. Phagocytosis of nanoparticles may result in reactive oxygen species (ROS) which are toxic to cells [38-40]. It has been reported that not only metal nanoparticles are toxic to macrophages, but some metal corrosion products, such as chromium orthophosphate, are also potent macrophage/monocyte activators and are therefore likely to contribute to macrophage release of inflammatory factors [38,41,42].

The molecular mechanisms and gene expression events involved in the cellular responses to metal nanoparticles and consequent cytotoxicity to phagocytes and surrounding tissues are largely unknown. An understanding of gene expression and regulatory pathways involved in metal nanoparticles-related cytotoxicity, both *in vitro* and *in vivo*, is therefore a fundamental step towards development of early diagnostic tools and treatment paradigms.

After phagocytosis, the phagocytosed materials will be stored in phagosomes and subject to digestion/degradation. In the case of metal particles they should be subject to corrosion. Corrosion of metal nanoparticles within cells is still poorly understood. In theory, metal corrosion can be expressed as a generic chemical formula:

$M \rightarrow M^{+} + e^{-}$

Where M is the uncharged metal atom at the metal surface, M^{+} is the positively charged metal ion (oxidised) which may dissolve in solution and e^{-} is the electron that may remain in the metal, or be consumed by a reduction reaction. (http://www.corrosionist.com/Corrosion_Fundamental.htm)

Metals and metal alloys used for orthopaedic implants are believed to be highly corrosion-resistant [43]. These metals are protected by a thin film of oxide which prevents further corrosion of the metal under normal conditions.

Metal corrosion is the process of releasing metal ions into solution. Under normal circumstances, weak acid may dissolve the oxides on the surface of a metal, but it will be difficult to dissolve the metal itself. In an environment with oxygen, new oxidized film will soon form and protect the pure metal from exposure to the environment. Due to the protection of the thin film of oxides on the surface, the metal cannot be further oxidized, therefore not subject to further corrosion.

However, metal implants in the body are not in a normal condition. They are in a nearly perfect environment for metal corrosion: warm (37°C), humid, rich in oxygen and may experience extremely acidic microenvironment. A mixture of an acidic environment and the presence of an oxidant may break through the protective barrier.

Phagocytes, in particular macrophages, are strong producers of an acidic environment via their proton pump (H^{+}-ATPase), and also produce reactive oxygen species (ROS), such as H_2O_2, and superoxide anion (O_2^{-}), via NADPH oxidase. Phagosomes in macrophages are therefore acidified and enriched in ROS, thus providing an ideal environment and the driving force for continuous corrosion of metal nanoparticles. Furthermore, metal wear debris is micro- or nanometre sized and therefore more active due to its greatly increased surface area.

Corrosion of metal nanoparticles releases metal ions, such as Co^{2+}, Cr^{3+}, Ti^{4+}, and Cr^{6+}. Although the overall metal ion concentration in tissues surrounding metal implants may not reach *in vitro* cytotoxic levels, they can accumulate within phagocytes to a level that is sufficient to kill the phagocytes [44]. In addition, oxidation of metals is believed to produce additional ROS, which are toxic to cells and lead to damage to DNA and lipids. Other metals may also produce nanoparticles after implantation, such as tantalum rods [45], but there are no available reports regarding the consequences of cellular exposure to these nanoparticles.

Metal ions may not exist in the body as free form, but more likely to bind to proteins [46-48], form oxide or salt [49].

Comprehensive screening of implantable metals for nanotoxicity and related gene expression in cells and tissues is an important approach to explore the activity of new pathways and molecular mechanisms.

Concluding Remark

Implant metal wear and corrosion-related complications remain a major cause of implant failure. In the case of MoM hip arthroplasty, over the world there are still more than a million cases who have already had the implants. It is unlikely to replace metal components in joint replacements and other uses in the foreseeable future. To understand the adverse tissue responses to metal implants is still apparent, and important both in basic and clinical research.

The key questions need to answer can be list as the following:

1. Are all metal nanoparticles toxic to macrophages, or are some less toxic than others? Can inhibition of cell-mediated corrosion of metals reduce cytotoxicity?
2. What is the missing link between metal debris and lymphocyte infiltration with subsequent severe immune/allergic and inflammatory responses?
3. Which genes are expressed more abundantly in macrophages in response to metal nanoparticles? Are there de novo gene expression pathways linked to cytotoxicity of metal nanoparticles? Is there expression of any material-specific genes (in response to different metals)?

Further research is warranted to shed light in the mechanism of metallosis and related clinical complications.

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