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Review

Immune reactions induced by metal-on-metal arthroplasties. The role of type IV delayed hypersensitivity and its clinical implications

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Abstract. Introduction: Total joint arthroplasty plays an essential role in the treatment of advanced forms of arthrosis. Unfortunately, the metallic by-products resulting from the prolonged use of the metal-on-metal (MoM) implants, can lead to mild or even severe immune reactions. This immune reaction, studied intensively in recent years, can cause undesirable local and systemic reactions and therefore is an important cause of long-term implant failure. Due to the high long-term failure of this type of implants, Highly Cross-Linked Polyethylene and ceramic weight bearing components have gradually taken their place. While some intricacies of the immune pathway still elude us, there is an ongoing process of standardization of care for patients that wear a MoM Total Replacement Implant or MoM Total Resurfacing Implant System. Materials and methods: To identify relevant literature, we researched the MEDLINE database via the PubMed interface. The search string used comprised of one or more of the following words/structures: aseptic, osteolysis, loosening, metal induced, metal ion, dermatitis, delayed type hypersensitivity, ALVAL (aseptic lymphocyte-dominant vasculitis-associated lesion), and implant related immunity. Results: This narrative review summarizes data on immune reactions occurring in orthopedic metallic implants and the clinical implications of this type of reactions. The article describes the clinical manifestations, their progression and the mechanisms involved in these manifestations. Conclusion: In conclusion, this review challenges one of the major causes of long-term implant failure in total joint arthroplasties, describing the clinical manifestations and implications of the delayed type immune reactions to MoM implants and proposing the use of a check-up algorithm in patients wearing a MoM hip arthroplasty.

Key Words: Delayed type hypersensitivity, type IV hypersensitivity, orthopedic metallic implants, aseptic osteolysis, metal-on-metal arthroplasty.

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Introduction

Total joint arthroplasties performed at multiple sites such as hip, knee, shoulder and ankle, are part of the current surgical practice and are most often used in the treatment of advanced arthrosis. Unfortunately, some complications may limit the lifespan of this type of implant. The occurrence of aseptic osteolysis and other local aseptic complications may lead to aseptic loosening and ultimately to instability at the bone-implant interface (Abu-Amer et al 2007, Drummond et al 2015).

The pathophysiology of the aseptic osteolysis process and of prosthetic instability (Figure 1) is caused by the chronic inflammatory response initiated and maintained by metallic microparticles resulting from mechanical wear of the prosthesis. In this inflammatory process, multiple cells are recruited to maintain inflammation, such as: macrophages, fibroblasts, giant cells, neutrophils and lymphocytes; last but not least, (Holt et al) 200 osteoclasts are recruited, having a primary role in bone lysis It is also suspected that these recruited cells secrete multiple molecules that promote osteoclast activity (Abu-Amer et al 2007).

Materials and methods

To identify relevant literature, we researched the MEDLINE database via the PubMed interface. The search string used comprised of one or more of the following words/structures: aseptic, osteolysis, loosening, metal induced, metal ion, dermatitis, delayed type hypersensitivity, ALVAL (aseptic lymphocyte-dominant vasculitis-associated lesion), and implant related immunity (Figure 2).

Results

The pathophysiology mechanism of delayed-type hypersensitivity

Even though the main focus of this article is the delayed immune reaction, it is also important to note that there is a close connection between the innate immune response and the acquired one. Regarding the hosts reaction to metallic implants, the innate immune response is the first to react and is the provider of antigen presenting cells (important in the sensitization stage). Type IV hypersensitivity is a cell-mediated immune response. Most type IV immune responses are limited and of low intensity, but there are also exceptions to this rule (Merritt et al 1996).

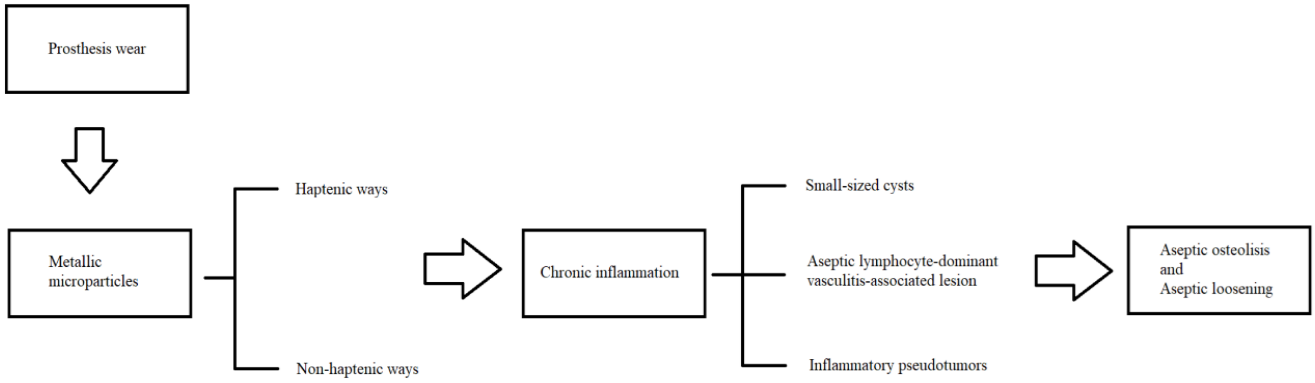

Fig. 1. Pathophysiology of aseptic osteolysis and prosthetic instability

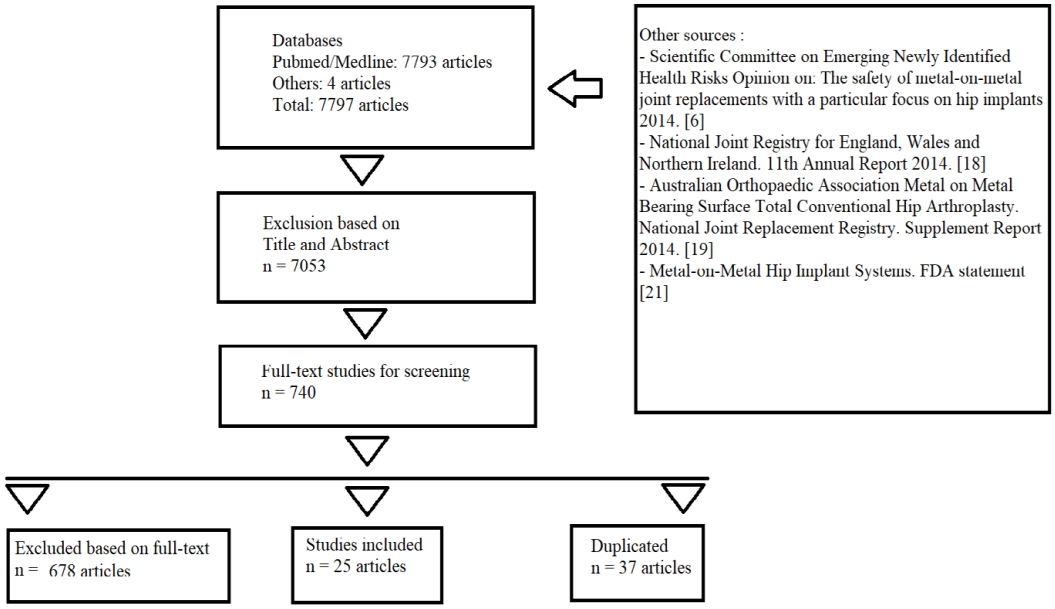

Fig. 2. Search strategy and flow diagram for database search

The delayed-type immune response typically consists of two stages: (1) A stage of sensitization, where the metallic particles with immunogenic properties are captured and processed by an antigen presenting cell, which will then be presented to naive T lymphocytes. Naive T lymphocytes will later differentiate into sensitized T lymphocytes. (2) An effector stage; this step will trigger a new contact with the antigen to which T lymphocytes have been pre-sensitized. After a period of more than 48 hours, lymphocytes will act based on their subtype. T helper subtype lymphocytes will release cytokines; while cytotoxic lymphocytes will release cytotoxic protein.

The most common metal particles forming immune complexes with self-proteins are nickel, chromium, cobalt and beryllium particles (Liden et al 1994). Metallic particles with immunogenic properties may also influence the inflammatory process in an indirect manner. Some authors have shown that there are alternative ways in which metal particles can activate the immune system by non-haptenic mechanisms; this leads to the possibility of activating tyrosine kinases involved in T cell activation (Griem 1995, Nakashima 1994). However, despite these alternative pathways, delayed hypersensitivity remains the dominant mechanism when it comes to implantology.

In addition to the direct sensitizing effect of metallic implant degradation products, other intricate effects may also arise. Similar to cross-reactivity occurring with other allergens, a type of cross-sensitization can also appear in the case of metals, the best-known example being between nickel and cobalt (Basketter et al 1993, Merritt et al 1996).

One of the adverse reactions to metallic implants may be the development of peri-implant osteolysis (SCENIHRO 2014). Although the physiopathogenic mechanism that leads to the reduction of bone density in the proximity of the implant is not fully known, it is accepted that cytokines and pro-inflammatory factors released in the local chronic inflammatory process play an essential role in the development of osteolysis. Many cytokines such as interleukin 6, interleukin 1, prostaglandin E2 and TNF alpha promote the genesis of osteoclasts (Holt et al 2007).

However, they are not the main factors leading to the maturation and differentiation of osteoclasts. There are recent studies indicating that the RANKL-RANK-NF-B pathway has a primary role in the osteoclastogenesis process. This pathway also has implications in the development and function of the immune system (Holt et al 2007). Given the multiple functions of the RANKL-RANK-NF-B pathway, one can suspect the common link between the immune system and osteolysis secondary osteoclastogenesis processes (Holt et al 2007).

Local and general implant-related manifestations of delayed-type hypersensitivity

Symptoms induced by metal hypersensitivity are diverse and often manifest in subtle ways. Since metallic microparticles have an immunogenic role, sensitization to these particles can cause both local and systemic reactions.

On a systemic level, skin damage caused by metallic immunogenic particles falls under the category of metal hypersensitivity-induced dermatosis (MHID). Typical manifestations of these dermatoses are urticaria and eczema; the affected skin surface may range from limited forms such as dyshidrotic eczema limited to hands and feet (Vien et al 2018), to extensive skin manifestations such as cases of erythroderma (Vien et al 2018).

The role of metal-induced toxicity in other systemic pathologies is controversial and there are few studies evaluating the carcinogenic potential of orthopedic metal implants. For example, there is no concrete evidence that "metal-on-metal" hip resurfacing arthroplasties (MoM HRA) can lead to an increase in the incidence of malignant pathologies (SCENIHRO 2014). Moreover, in the case of pregnancy, although the trans-placental passage of metal ions has been demonstrated, no teratogenic effect has been proven so far (SCENIHRO 2014). Patients with metal alloy implants have higher urinary levels of metal ions (SCENIHRO 2014). However, a study by Van Lingen et al. (2013) did not identify significant neurological, cardiac, thyroid or renal impairment over a 4.2-year period in patients with MoM hip arthroplasties and elevated cobalt serum levels (van Lingen 2013).

On a local level, the immune response triggered and maintained by metal particles may result in various forms of immune response organization. These forms may range from asymptomatic small-sized cysts to large masses, named by some authors inflammatory pseudotumors (SCENIHRO 2014). The time interval during which these manifestations may occur can vary widely, so therefore local complications can be categorized based on the time elapsed from implantation, as follows: immediate, medium and long-term local complications (SCENIHRO 2014).

The term "inflammatory pseudotumor" was introduced to describe the organization of tissues affected by inflammation as into an aseptic mass located at the periprosthetic level. This form of organization can take both solid and liquid form and is associated with clinical, imagistic and histopathological signs of inflammation.

Periprosthetic inflammatory reactions also affect blood vessels, leading to aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL). The main mechanism of this vasculitis is suspected to be type IV delayed hypersensitivity. The immunogenic particles involved in this type of vasculitis are metallic microparticles resulting from erosion of the orthopedic implant, particularly cobalt and chrome particles (Watters et al 2010).

The presence of ALVAL is of particular importance when assessing failure of metal-on-metal implants, but despite this, many screening methods used to evaluate this type of vasculitis are unreliable. Although serum levels of metal ions are routinely elevated for MoM implants, these elevated serum levels do not seem to correlate with the severity of lesion-associated aseptic vasculitis. The increase in monocytes in the synovial fluid may be useful in the diagnosis of ALVAL and is indicative of a delayed type hypersensitivity reaction (Plummer et al 2017).

Given the multitude of implant wear-induced lesions, a term to encompass all the pathological changes that occurred at this level was necessary. Metallosis is defined as local necrosis, aseptic fibrosis or loosening of an implanted metallic device resulting from corrosion and release of metallic microparticles (Langton et al 2011). There is a possibility that the notion of inflammatory pseudotumor refers to an advanced stage of the metallosis process, thus chronic persistence of local inflammation and aseptic vasculitis damage may lead to this pathogenic end stage (Langton et al 2011).

Clinical implications

In recent years, the level of awareness regarding immune potential of metals has improved. Many studies look into the sources of metallic microparticles capable of inducing hypersensitivity reactions. A literature review by Basketter and colleagues concludes that common products containing nickel, cobalt and chromium particles contain few quantities of these particles and have far little contact time to induce hypersensitivity. The authors conclude that when it comes to the sensitized patients, the focus should be on other sources of exposure, such as jewelry and other metallic objects. Despite these findings, good manufacturing practice of these products limits the concentration of the respective metals to less than 5 ppm (parts per million mg/L) as the maximum value, whereas the target value should be below 1 ppm (Merritt et al 1996).

Other objects that can induce hypersensitivity to metals of medical interest are implants made of metal alloys. The most commonly used metal implants in the field of orthopedics are: stainless steel - alloy made of nickel, chromium and a small amount of molybdenum; cobalt alloy - contains cobalt, chromium and small amounts of nickel and molybdenum; and titanium alloys made up of titanium, aluminum and vanadium (Hallab et al 2001). Testing for sensitivity to constituent particles should therefore be targeted depending on the type of alloy used in the arthroplasty, and should be performed for all patients that undergo such a procedure.

Arthroplasties made with MoM prostheses have some structural advantages over polyethylene (MoP - metal-on-polyethylene) components. The material from which the MoM is built gives them increased resistance over time not only due to the high durity of the material but also by because of the ability to mold very smooth joint surfaces. A study by Cuckler et al. (Cuckler 2005) reveals an annual wear rate in the case of MoM hip arthroplasty varying between 1 and 5 microns per year.

However, MoP arthroplasties exhibit wear ranging from 100 to 200 microns per year. The excretion of metal ions resulting from the hip MoM arthroplasty is performed through the

kidneys and subjects with the prosthetic implant presented serum levels that were 3-5 times higher than those of the control group. In the same study, no adverse physiological effects were found in patients exposed to cobalt-chromium implants at a long-term follow-up.

In addition to the lower wear rate in hip arthroplasty performed with MoM, this type of arthroplasty also has other advantages such as a lower osteolysis degree compared to MoP convective couplets. The lower rate is attributed to a lack of polyethylene particles (Cuckler 2005), the absence of prosthetic component fracture, a reduced number of dislocations (Drummond et al 2015) and the ability to use larger diameter femoral heads, which adds stability to hip arthroplasty (Cuckler 2005).

A common rationale for preferentially using MoM arthroplasties lies in their long lifespan. However, data from the National Joint Registry of England, Wales and Northern Ireland (2015) show that the 10-year revision rate is 19.68% and 21.92% for cemented and non-cemented MoM arthroplasties, respectively (NJR 2014 www.njrrerorts.org.uk). In the case of total MoP hip arthroplasty, the 10-year revision rate is 3.13% for cemented and 3.98% for non-cemented. (www.njrreports.org.uk 2014) The higher revision rate for hip arthroplasty performed with MoM was correlated with pathology related to exposure to metals in nearly 40% of cases (AOA 2014).

In the case of MoM arthroplasty, the incidence of local complications is not unitary. A variety of prosthesis-related factors may influence the severity of the local response, such as head size. For instance, larger hip arthroplasty heads (head > 40 mm) are associated with a higher revision rate (AOA 2014). Also, various prosthesis brands have different revision rates at 10 years (www.njrreports.org.uk 2014). In addition to prosthesis-related features, some properties of the wear particles can also influence revision rate. Hallab and colleagues (Hallab et al 2009) identified that the inflammatory response is more pronounced in cases where the particle size is larger. Moreover, phagocytizable particle concentration, higher particle length (fiber-like particles) and higher particle chemical reactivity are related to a more pronounced pro-inflammatory effect. The latter points to the idea that the polymer particles may be less toxic than the metal particles, but there is no consensus in this case (Hallab et al 2009).

When choosing an implant type, it is thus recommended to weigh the benefits of MoM arthroplasty against the risk of developing local adverse reactions that may shorten the implant's lifespan. Choice of implant type should be made after a thorough evaluation and the risk/benefit analysis should take into account patient features such as age, gender, physical activity, occupation etc. (SCENIHRO 2014)

According to FDA guidelines, patients with MoM hip arthroplasties and implant-related symptoms should immediately address an orthopedic surgeon (www.fda.gov).In addition to a clinical exam, symptom evaluation can include joint fluid analysis sampled through needle aspiration, soft tissue imaging and blood tests that also check for metal ions. Currently, the FDA does not recommend routine surveillance for these patients, but in the case of hip arthroplasty patients, an annual or bi-annual check is recommended.

Discussions

Testing methods and their clinical applications

Given the many clinical implications of delayed-type hypersensitivity in orthopedic implants, the issue of prior testing for atopic terrain and the utility of these tests for patients who have developed adverse reactions that suggest delayed-type hypersensitivity has been raised.

The main test methods used are in vivo methods: patch test and the intradermic reaction; and in vitro methods: lymphocyte transformation test and the lymphocyte migration inhibition test. In addition to the test methods mentioned above, delayed-type hypersensitivity is also studied by determining the levels of metal ions in the biological fluids of patients with metallic implants. The review by Rosner et al. (Rosner et al 2017) states that at the present time, the consensus is that pre-implantation patch testing for individuals without metal induced skin lesions or a history of other side effects to metallic implants is not necessary. The patch test may be helpful in supporting the diagnosis of hypersensitivity induced implant failure or dermal damage, if they are unexplained by other causes, such as infectious or biomechanical issues (Rosner et al 2017, Thyssen et al 2011). In the context of day-to-day clinical practice, patch test is commonly used due to its low cost and easy use.

Despite the advantages of patch testing, this method also has its limitations. There are multiple factors that lead to patch testing inadequacy such as the competition of various metal ions to bind to serum proteins (Yang et al 1994) and the fact that the patch test does not perfectly simulate the immune pathways that lead to metallic implants hypersensitivity induced reactions. Thus, patch testing differs from implant related reactions in multiple ways: time of contact with the allergen, the environment where it is applied: skin surface vs. internal biological environment and many other factors related to the particularities of the individual's immune system.

As for the in vitro methods, although there are studies suggesting that in some clinical contexts they could provide more information than in vivo tests (Carando et al 1985), this method of testing has not seen much use due to its high cost and difficulty of use.

Although pre-implantation testing is debatable, especially for patients with no prior side effects to the metals in question (Rosner et al 2017), testing for type IV hypersensitivity reactions after the metallic implant has been placed is becoming a routine practice. Determining blood metal ion abnormalities is becoming part of the follow-up screening for patients with MoM hip arthroplasties, as seen in Figure 3.

Data from the literature (Drummond et al 2015) indicate that serum levels of metal ions are higher in patients with metallic arthroplasty, especially cobalt and chromium. Also, patients with MoM have higher levels than those with MoP or MoC (metal-on-ceramic) (Drummond et al 2015). The clinical significance of these findings remains an important subject of discussion. Researchers are seeking to find a link between high ionic concentration levels and clinical manifestations, as well as trying to establish the threshold levels within this context.

One of the main limitations of this review is the fact that MoM arthroplasties, as mentioned before, are becoming less used (www.fda.gov). In recent years, the research regarding the applicability of MoM implants has significantly reduced.

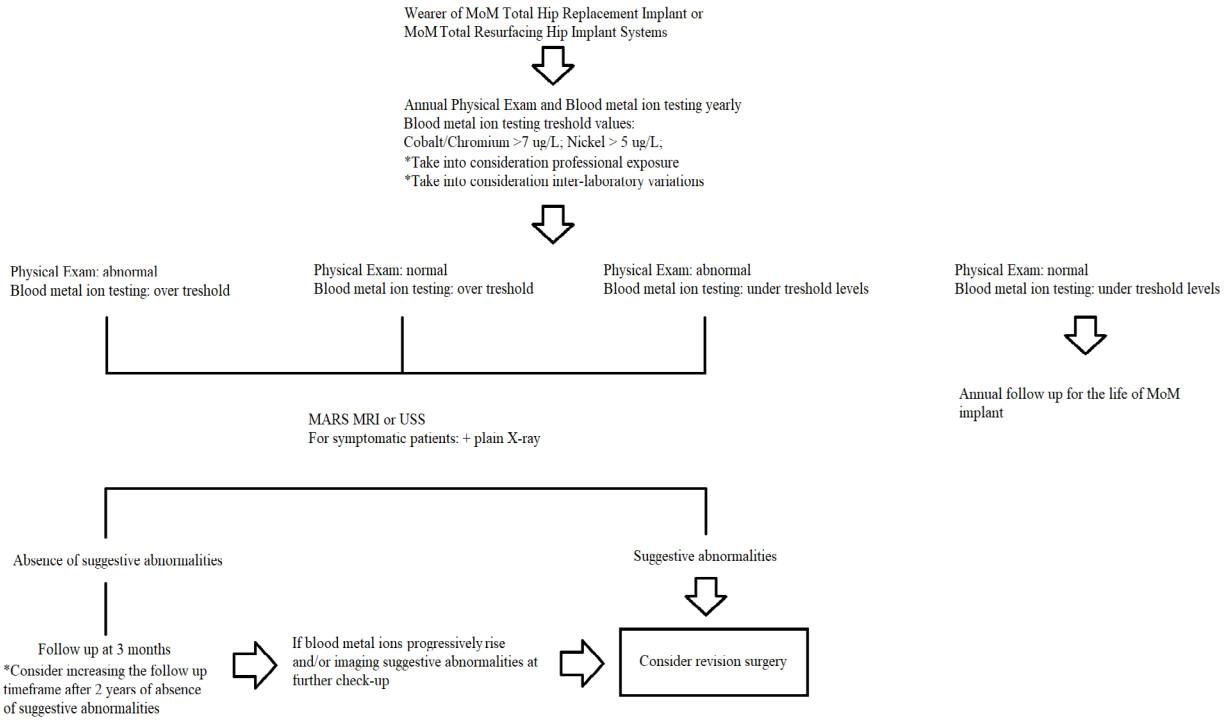

Figure 3. Local check-up protocol for patients wearing a MoM Total Replacement Implant or MoM Total Resurfacing Implant System. *Consider LTT testing in selected cases

Conclusions

In conclusion, metal hypersensitivity has a fundamental role in the development of local and systemic aseptic complications occurring in with implants made of metal alloys.

The detailed description of the mechanisms by which peri-prosthetic inflammation is triggered and maintained can help diagnose and treat the complications of the implantable devices in question. Thus, lifespan of these devices and patient quality of life can be improved.

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