

# Metal hypersensitivity after knee arthroplasty: fact or fiction?

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**Summary.** *Background and aim of the work:* Hypersensitivity to metals in the general population has an incidence of about 15%, and is rising also for the higher number of joint replacements in the last decades. Total Knee Arthroplasty (TKA) represents the most performed orthopaedic procedure during last years, and it seems to be particularly associated with sensitization after surgery. On the other hand, there is a rising amount of patients with painful but well implanted and functioning TKAs: in certain cases, after the exclusion of the most frequent causes of failure, a condition of hypersensitivity may be found, and a revision with anallergic implants is mandatory. The present study is a review of the potential problems related to hypersensitivity in TKA, its possible diagnostic procedures, and the surgical options to date available. *Methods:* Medical history, patch testing, and other specific laboratory assays are useful to assess a status of metals hypersensitivity before surgery in subjects undergoing a knee replacement, or even after TKA in patients complaining pain in otherwise well implanted and aligned prostheses. However, few groups worldwide deal with such condition, and all proposed diagnostic protocols may be considered still today conjectural. On the other hand, these represent the most updated knowledge of this condition, and may be useful for both the patient and the orthopaedic surgeon. Once assessed a possible or ascertained allergy to metals, several options are available for primary and revision knee surgery, in order to avoid the risk of hypersensitivity. *Results:* A review of the recent publications on this topic and an overview of the related aspects has been made to understand a condition to date considered negligible. *Conclusions:* Hypersensitivity to metals has not to be nowadays considered a “fiction”, but rather a possible preoperative risk or a postoperative cause of failure of TKA. Crucial is the information of patients and the medical history, associated in suspect cases to laboratory testings. Today in the market several knee implants are available and safe for allergic patients undergoing TKA. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** hypersensitivity to metals, total knee arthroplasty, anallergic implants, oxidized zirconium, all polyethylene, PVD, primary joint replacement, revision, patch testing

## Introduction

Hypersensitivity to orthopaedic implants is today a matter of debate. It is well known the phenomenon of hypersensitivity to metals, particularly to nickel, in 10-15% of the general population (1-3). Nickel is normally present in many objects and substances of daily life. The classical clinical expression of this sensitivity is represented by a series of effects such as dermatitis,

rash, erythema and rhinitis; rarely, general complications may occur such as itching or asthma (4-6). In the orthopaedic field, subjects candidate to a joint replacement should be studied for any condition that may be conducted to an allergy to metal components. Moreover, in patients operated for a joint arthroplasty complaining postoperative pain, swelling, bone resorption, and skin necrosis may also represent clinical signs of hypersensitivity to metals (4, 7-12). Recently, early

failures of orthopaedic implants have been associated to mechanical loosening related to the indirect activation of macrophages by metal ions released after contact with host fluids (4, 7, 13). "Aseptic lymphocyte-dominated vasculitis-associated lesion" (ALDVAL) or "Lymphocyte-Dominated Immunological Answer" (LYDIA) are common terms indicating these suggestive but not pathognomonic manifestations of an altered response to metals (14, 15). In some report, conditions of sensitivity to metals have been successfully managed by the removal of the metal devices (7, 16), while in other experiences the reactions persisted also after the removal (16). Surprisingly, patients with ascertained hypersensitivity to metals did not present any reactions after joint replacements with a low to moderate nickel content (17). These data support the idea that hypersensitivity to metals is a very complex phenomenon that has several risk factors and unknown mechanisms and clinical features still to be cleared.

Metal ions released as the result of wear of knee implants are accumulated in the periarticular tissues and carried through the bloodstream to emunctory organs (15, 18-20). Bound to serum proteins, metal ions form hapten-like complexes that may be identified by the immune system as antigens, activating local or systemic reactions by the recruitment of inflammation cells. This reaction (classified as a type-IV delayed hypersensitivity and mediated by antigen-presenting cells and T lymphocytes) produces high release of pro-inflammatory and osteoclastogenic cytokines (20, 21, 24). T-cell activation produces a self-perpetuating loop activating other cells, as macrophages that by phagocytosis (commonly associated with expression of MHC II) and depending of size, shape, and quantity of the debris, may induce symptoms of allergic dermatitis and even periprosthetic loosening (13, 20, 25).

The methods to assess such processes are still debated and not widely diffused. Several diagnostic procedures have been proposed over the decades: Patch Testing, Lymphocyte Transformation Test, Migration Inhibition essay, Lymphocyte Activation Test, Confocal microscopy, measurement of cytokines release by the enzyme-linked immunosorbent assay on lymphocytes cultures, and Memory ELISA (3, 9, 20, 24, 26-28). No one of such essays result as ideal alone, but combination of two or more of them may give a quote

of probability of a status of hypersensitivity to metals in the studied subjects (20).

In the case of persisting pain after TKA, it is mandatory to exclude the most common causes of failures (mechanical loosening, infection, and instability): if none of these causes arise from the standard diagnostic pathway, other uncommon sources of pain should be assessed (10, 11, 29). Among these, hypersensitivity is surely to be taken in account, even if rare. Metal components and cement elements may both be causes of recations. While allergy to cement elements as p-toluidine, benzoyl peroxide, or methyl methacrylate is substantially more than sporadic (also for the frequent use of cementless implants), the number of patients with reactions to metals is rather uncommon, but it will probably raise due to the worldwide dramatic increase of total knee arthroplasties (TKAs) during last decades, and surely maintained in the next years (20, 30). For this reasons, recently many companies have provided the manufacture of metal alloys with untraceable nickel content or Cobalt-Chrome implants with multistratified non-allergenic coatings in order to avoid any risk of sensitivity (31-37). To date, no substantial clinical differences on the outcomes have been found between high-performance nickel-free implants (oxidized zirconium, titanium, or ceramic femoral components articulating with all-polyethylene or titanium tibial components) and hypoallergenic implants (nitrogen-ion implanted mechanisms, diamond-like-carbon, and physical vapour deposition - PVD coatings) (38-41).

The present chapter is an overview of the literature related to the risk of hypersensitivity to metals in patients undergoing TKA or with painful TKA, and related aspects of diagnosis and treatment.

### **Diagnostic assessment of hypersensitivity**

Subjects needing a TKA with known or suspect allergy to metals or in case of painful knee implants (after exclusion of the most common sources of failure), a medical history should be widely analyzed with the patient (9, 29). It is known that a careful series of questions about a possible sensitivity to substances may be positive up to 15% of the general population:

it is thus considered crucial a full information about a not insignificant risk of allergy in subjects undergoing an orthopaedic implant. Attention should be paid to any familiarity for immunological diseases, drugs allergy, associated comorbidities, and their related medical therapies. Patients with previous dental surgery may have been in contact with metals for the first time. Similarly, many subjects may be sensitized to nickel or other metals by specific working activities: painters, cleaning companies, or leather factories workers, and even metal factories workmen (10, 11). Then, such patients should undergo two or more of the previous mentioned diagnostic procedures (9, 20, 42, 43). In patients with a positive medical history, the most common used approach is Patch testing (PT). Such examination may be performed for metals but also for cement components, by adhesive patches loaded with known concentrations of specific allergens compared with Vaseline. PT is a widely used tool that presents gross limitations: skin reactions are different compared to deep tissue layers and joint environment, and antigen-presenting mechanisms may be therefore altered. Moreover, PT has different preparations and haptens plots, thus may differ from subject to subject, and tester to tester (9, 20, 42, 43). Leucocytes Transformation test (LTT) and its modern variant (MELISA) consists in the evaluation of [3H]-thymidine uptake in lymphocytes after contact with specific allergens (12, 28, 42, 43). The Leukocyte Migration Inhibition test (MIF) measures the speed of migration of leukocytes after contact with sensitizing allergens (12, 20). The lymphocyte activation test (LAT) quantifies the expression of specific receptors (CD69) on circulating mononuclear cells after stimulation with metals (12). ELISA testing allows the measurement of cytokines released by stimulated cells: however, most of such cytokines may be overexpressed also for other conditions or diseases, and their amount may not be related exclusively to hypersensitivity (20, 43). Confocal microscopy is performed to evaluate intracellular abnormalities after contact with metals by 3D images of the stimulated cells, obtaining optical slices reconstructed by Computer Tomography: it is a very interesting tool even if not widely diffused (43). Despite all of them may be considered objective tests, they still lack of a routine validation (12, 20, 43).

A high suspect of hypersensitivity to metals may be thus strongly considered when medical history, PT and other laboratory findings are positive. It may be considered as possible when medical history and patch testing are positive, but blood assessments are negative (43). Finally, but of paramount importance, it is clear that every subject may have unknown preoperative conditions that may induce their sensitization after surgery, and this is the reason to be careful in the exclusion of potentially risky situations before TKA or, in case of painful implants, to assess any cause of pain after a joint replacement, other than the classical aseptic loosening, infection, and instability.

### **TKA and hypersensitivity to metals: available options**

Once a patient needing a TKA is addressed as allergic or potentially sensitive, an adequate implant should be used. Two are the available options: non-allergenic or coated implants. The first type is characterized by components made of inert materials without any immunogenic activity: oxidized zirconium, pure titanium, or ceramic femoral components coupled with all-polyethylene or titanium tibial components are the typical solutions. Several series using these systems have been reported with good outcomes (31-37), even if very few experiences have reached a mid- to long-term follow-up (33, 38, 43-45). The second type is represented by implants with standard Cobalt-Chrome components coated by one or more layers of immunogenic-inert substances (nitrogen-ion implanted mechanisms, diamond-like-carbon, and physical vapour deposition coatings). Several releases in literature demonstrated that also these materials have a good short-term mechanical behaviour with no cases of hypersensitivity (34). There is still today a debate whether a coated implant may undergo at long-term wear with release of particles both from the inert and Cobalt-Chrome layer, inducing a delayed sensitivity or loosening: this phenomenon should be observed and evaluated in the future (34).

Another scenario is represented by patients with a painful TKA (defined as a well-positioned, stable, and aligned implant associated with pain and functional limitation persistent for six months after surgery) due

to hypersensitivity to metals. In such cases, when a prosthesis had induced an immunogenic reaction, a revision with a non-allergenic implant is mandatory. However, few are the revision systems with adequate features in the market. It may be used a single revision system characterized by oxidized zirconium femoral component, titanium tibial plate, titanium stems and wedges (38), or few implants with PVD-coated femoral and tibial components, stems, and wedges (34).

Independently by primary or revision surgery, the choice of an implant for sensitive patients may prevent any kind of potential reactions, ensuring on the other hand good survival rates and kinematic properties comparable to standard prostheses: this is related to the high tribologic performances of these modern prostheses.

## Discussion

A great number of TKAs is every day performed worldwide with good results and high satisfaction referred by patients (30, 35, 46, 47). It is very probable that in the last decades patients with known or unknown allergy to nickel or other metals might have reported satisfactory outcomes after TKA with standard implants with nickel, cobalt, and chrome content (17). Nonetheless, it is well known that several subjects, allergic to metals have presented local or general reactions after contact with orthopaedic devices or implants until their removal (43). Furthermore, cases of persistent reactions have been described yet after the removal of devices and hardware with high content of sensitizing metals (16). Finally, well implanted and aligned knee replacements, showing no suspect of loosening, infection, or instability, are referred by some patients as persistently painful: this condition may be associated to a reaction of the host tissues to metal components (9, 43). All these facts show that the phenomenon of hypersensitivity to metals exists and has not to be ignored, but it is on the other hand very complex and challenging.

It is reasonable to assess any risk of hypersensitivity in subjects undergoing a joint replacement, and in case of known allergy or suspect, some testings have to be performed. Patch testing, LTT, LAT, MIF, MELI-

SA, ELISA, confocal microscopy are examples of procedures that have been considered useful for such purposes. However, their contribution is still to date thought to be imprecise and debated, due to the lack of reproducibility (12, 42). If two or more of such assays show a positivity and the medical history is suspect or positive, a reasonable high risk of hypersensitivity should be addressed (43).

In such conditions, a primary TKA with no content of sensitizing metals should be implanted, as similarly, in case of a painful TKA in a patient considered sensitive postoperatively, a revision knee prosthesis with non-allergenic materials should be proposed. Nowadays, in the market several implants show adequate features useful for such patients. Most of these prostheses have been released years ago, and several series have been published showing good outcomes and patients' satisfaction (31-41).

Even if data from the few experiences of the most active groups involved in the study of this phenomenon indicate that the actual incidence of hypersensitivity to metal implants is estimated to be lower than 1% of the overall population undergoing TKA (12, 43), it has to be carefully excluded when proposing a joint replacement to a patient (20, 43). Tools as patch testing or laboratory methods have to be adopted in case of suspect (12, 20). When the suspect is strong, the choice of the implant has to be taken individually, in a case-by-case fashion. The best scenario that the orthopaedic community is awaiting in order to avoid hypersensitivity is the detection of specific predictive biomarkers in patients candidate to TKA.

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