Review paper

Metal hypersensitivity in hip, knee and spine surgery

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Abstract

The number of implanted joint prostheses and damaged spinal components is steadily increasing. At the same time, rejection of the implanted material is observed in operated patients, which manifests itself in both skin and general reactions, as well as loosening and earlier wear of implanted prostheses, which was previously referred to as aseptic reactions. However, it has been shown that in a significant proportion of patients, rejection of implanted material may be caused by hypersensitivity to a specific metal. For this reason, patients qualified for implantation of foreign material, mainly nickel, titanium, chromium, molybdenum, and other alloys, should be subjected to allergy tests to detect possible risks in the form of metal sensitivity reactions.

Key words: metal hypersensitivity, spine surgery, hip and knee prostheses.

Introduction

Modern medicine cannot be imagined without the possibility of implanting joint prostheses, damaged spinal components, or artificial heart valves. However, the material from which these stabilizing elements are made may be also immunogenic, fortunately these reactions are not common [1]. However, the presence of cutaneous and systemic hypersensitivity in patients after knee arthroplasty [2–4] and a demonstrated allergic reaction to nickel, chromium and cobalt indicate that there is a problem in the treatment of patients with the use of implants, not only in orthopaedics.

The number of joint replacements performed annually in the USA exceeds 1 million. In 2010, the prevalence of total hip and total knee replacement was 0.83% and 1.52%, respectively. The number of procedures performed was higher in women than in men, and it increased with the age of the patient. Thus, as of 2010, nearly 7 million Americans live on hip or knee replacement [5]. Anyway, based on the analysis of the results of the implantation of the hip and knee joints included in the registers in Sweden, Norway, Finland, Denmark, Australia and New Zealand it was found that total hip and knee replacements showed revision rates of 6% after 5 years and 12% after 10 years [6]. Actually, the number of patients qualified for orthopaedic surgery increases and reveals the scale of the problem, especially in terms of complications, including allergic reactions to implanted metal prostheses.

Materials used in implants

The construction of the currently used joint prostheses is becoming more and more perfect, and the materials used show long-term durability. However, the materials they are made of may cause allergic reactions to metals and cement components. The list of implant materials (Table 1) is long and should be considered both before the surgery and when identifying any loosening of the prosthesis [7, 8].

Stainless steel commonly used in implants is an alloy composed of 17% to 19% chromium and 14% nickel, which makes the metal resistant to corrosion. In newer implants, molybdenum is also added, which creates a protective layer against the action of acids. On the other hand, titanium is added to implant alloys because it exhibits strength equal to steel and is 50% lighter. In turn, nitinol, which is an alloy of 55% nickel and 45% titanium, is characterized by high plasticity and is mainly used in vascular prostheses [9, 10].

As shown in Table 1, the most allergenic materials found in prostheses and orthopaedic components are cobalt, titanium, chromium, nickel and, more recently, zirconium. This indicates the need to pay attention to the type of material in the implant. Recently, more and more reports indicate the increasing scale of allergic reactions to titanium, which is widely used in implants, not only in orthopaedics. This may be induced since the exposure to titanium is also increasing, because it is found in watches, jewellery, body creams, make-ups, deodorants, toothpastes, and food [11, 12]. This requires increased attention to this component of implants in orthopaedic practice.

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Table 1. List of implant materials according to [7]

Implant	Elements	Percentage	Use
Stainless steel	Iron Nickel Chromium Manganese Molybdenum	40–68 8.3–35 20 2 2–3	Orthopaedic prostheses Pins, nails, bolts, screws, plates Surgical clips/ staples Cardiac/ intravascular devices
Cobalt-chromium-molybdenum steel	Cobalt Chromium Molybdenum Nickel Iron Manganese Tungsten Aluminium Titanium	60 27–30 5–7 < 0.5 < 0.75 < 1 < 0.2 < 0.1 < 0.1	Orthopaedic prostheses Pins, nails, bolts, screws, plates Surgical clips/ staples Cardiac/ intravascular devices Dental implants Restorations
Vitallium	Cobalt Chromium Silicon Manganese Molybdenum Iron	61 32 0.5 0.5 5.6 –	Orthopaedic prostheses Pins, nails, bolts, screws, plates Fixators
Titanium alloy	Titanium Aluminium Vanadium Nickel	90 5.5–6.5 3.5–4.5 0.012–0.034	Orthopaedic prostheses Pins, nails, bolts, screws, plates Fixators Surgical clips/ staples Pacemaker shells
Titanium-tantalum-niobium	Titanium Niobium Tantalum Zirconium	53 25 7 5	Orthopaedic prostheses
Nitinol	Titanium Nickel	55 45	Bone anchors, staples Cardiac/ intravascular devices
Oxinium	Zirconium Niobium	97.5 2.5	Orthopaedic prostheses

Causes of implant failure

The most common causes of implant failure include infections and mechanical issues of size, placement, orientation, or type of implant. The early failure is defined as < 2 years after the implant surgery, and late failure – 2 or more years after implantation [13].

The most frequent cause of knee prosthesis loosening is aseptic inflammation found in over 40% of revisions. On the other hand, the causes of early knee revision were infections in 38% of patients, loosening in 23%, instability in 6% and arthrofibrosis in 4%. Aseptic loosening of the implant was responsible for late revisions in 51.4% of the operated patients, which was preceded by infection in 22% of patients, instability in 10% and arthrofibrosis [14]. In another study the most common indications for hip replacement revision were aseptic loosening in 51% of patients, followed by instability in 15%, wear in 14%, and infection in 8% [15]. These above-mentioned observations were confirmed by the analysis of 2,107 patients after the first-time revision of total hip arthroplasty obtained from 30 centres in France, in which it was documented that the main reasons for the revision were mechanical loosening (42%), periprosthetic fracture (12%), infection (11%), wear/ osteolysis (11%), dislocation (10%), surgical technique error (6%), and implant fracture (3%) [16].

It is emphasized that poor outcomes for joint replacement may be due to comorbidities including diabetes, heart disease, smoking, osteoporosis, and other metabolic disorders. In recent studies, attention has been paid to the importance of sensitization to implant components as a reason for implant failure [13, 17]. Moreover, it has been shown that many elements of joint prostheses are made of materials which are highly sensitizing (Table 1).

Metal hypersensitivity in hip and knee prostheses

The first allergic reactions to the metal used in prostheses in patients undergoing hip replacement appeared relatively quickly. In 1940, Dr. Austin Moore performed the first hip replacement, and in 1968, the first total knee replacement [18]. However, it was not until 1974 that Evans *et al.* demonstrated that cobalt-chromium surfaces of implanted material release metal ions into local tissue, and then enter the bloodstream and exhibit a general effect [3]. It has been suggested that the released metal particles may cause necrosis of the bone and loosening of the implant because of the obliteration of local blood vessels. It was demonstrated in patients with loosening of a cobalt-chromium hip prosthesis and a knee prosthesis, in whom a positive reaction to cobalt, chromium and nickel was revealed in patch tests. The first documented description of cutaneous hypersensitivity (made in 1966) caused by a metallic orthopaedic implant concerned a patient with eczematous dermatitis as a reaction to a metallic plate used for fracture fixation [19].

The observations carried out indicate the allergic background of the observed changes, however, there are also data that document similar changes in joints for other reasons. In addition, not all patients with documented allergic reactions to metal report implant rejection. An illustration of such condition may be the case of a woman with preoperative positive patch testing to nickel, cobalt and chromium, who tolerated the cobalt-chromium knee prosthesis well for 2 years of follow-up [20].

In another study, patch tests to implant components were performed in 66 patients qualified for total hip replacement, in 53 patients with a stable prosthesis, and in 104 patients with prosthesis loosening. It was shown that the patch test results were not able to clearly differentiate patients in a stable state from those with implant rejection. Anyway, it has been shown that an allergic reaction to one element, mainly to bone cement, as well as the disclosure of earlier reactions to metals, had an adverse effect on the condition of patients and decreased the survival rate of total hip replacement [21]. In a subsequent study of 94 patients with a knee implant, including 47 with loosening of the implant, it was found that positive skin reactions to metals were different, but the highest (60%) in the loosening group [22]. It has also been shown that in patients with a history of positive metal allergy after total hip replacement, the average lifespan is reduced from about 120 months to 78 months [21], and the allergy to metal in implant in these patients may increase by about 6.5% after knee or hip arthroplasty [4].

Metal hypersensitivity in spine surgery

Metal hypersensitivity is very rarely indicated as a cause of complications after spine surgery. This problem is described in some case reports.

One of these is a patient with recurrent back pain after posterior lumbar decompression and fusion for lumbar disc herniation which was previously diagnosed as an aseptic loosening and an aseptic inflammatory response. The diagnostic patch tests revealed metal hypersensitivity as the cause of an aseptic loosening. Anyway, this patient gave a history of skin sensitivity to a metal watch and ring before spine surgery. During the revision, six pedicle screws were very loose off the vertebrae and lost their fixation function. Moreover, around the pedicle screw in the L4/L5 level a small granulation tissue was defined with infiltration of lymphocytes, fibroblasts and nanocapillaries which was not typical for infection but for an allergic reaction to metal [23]. In another case, 6 years after anterior lumbar interbody fusion there was a low back pain and abdominal pain with food intolerance. Presacral fluid collection was detected during the diagnostic process, infection was excluded, and patch test confirmed hypersensitivity to nickel. The change to polyetheretherketone interbody, without the presence of nickel, made it possible to control the described changes [24].

It should be emphasized that currently most of the alloys used in spine fixators have an oxidative layer to protect them from corrosion and the subsequent release of metal particles. Furthermore, spine implants may release metal ions and debris directly into the periprosthetic tissue [25]. Stresses and micromotion, as well as the action of the chemical factors from body fluids can damage the protective layer and release metal particles, which the organism reacts to in the form of an allergic reaction [26].

Titanium spinal implant hypersensitivity is very rarely described because the reactions reported by patients are not very specific. For example, anorexia and fatigue over a long duration after the initial post-operative period in a patient after the spinal fixation [27]. It has been shown in experimental studies that titanium particulate debris at the level of a spinal arthrodesis has the ability to release pro-inflammatory cytokines that cause increased expression of intracellular tumour necrosis factor α, increased osteoclastic activity, and cellular apoptosis [28]. The above-mentioned changes may explain both late-onset inflammatory-infectious complications and long-term osteolysis that are observed after spine fixations and are referred to as aseptic reactions.

The performed evaluation of the concentration of metal ions in blood after spinal arthrodesis were comparable to the concentration found after total joint arthroplasty [29]. However, these values were not of use indicator of hardware loosening or implant failure [30] but could point to the systematic reaction. Moreover, it has been shown that metallic spinal implants can cause allergic contact dermatitis even 15 years after arthrodesis. Nickel is the most common cause of these reactions, which can be confirmed with the skin patch test [26].

Mechanisms and diagnostics of allergy to metals

The released particles from the implant can become a hapten, which in combination with the proteins of the body has the ability to act on the circulating lymphocytes and develop a hypersensitivity reaction. You can expect an immediate humoral reaction with the formation of antibodies and immune complexes (type I, II and III reactions), but also a cell-mediated delayed-type (type IV) hypersensitivity response with the activation of Th1 lymphocytes in the peripheral lymphoid tissues [31]. This reaction results in the release of pro-inflammatory cytokines (i.e., TNF-α, IFN-γ, IL-1, and IL-2) which cause influx of inflammatory cells to the site of the implant [32]. As shown, this reaction differs from a typical type IV hypersensitivity reaction in that the presence of B lymphocytes, plasmocytes and massive fibrin exudation in the patient's tissue at the site of a loosened prosthesis, which is sometimes referred to as an aseptic lymphocytic vasculitis-associated lesion [33].

Increased rates of rejection of hip and knee implants as a result of an allergic reaction to metal leading to arthropathy prompted further research and analysis. Histological examination of patients with failed metal-on-metal (MOM) hip replacements revealed an inflammatory infiltrate at the implant site, dominated by macrophages, lymphocytes, and plasma cells along with severe fibrin deposition. The allergic reaction to cobalt, chromium, nickel, molybdenum, and manganese was confirmed in 81% [8]. During the research, the term aseptic lymphocyte-dominated vasculitis-associated le-

Table 2. Patch test panels recommended for patients qualified for hip and knee replacements according to [13]

Metals	Nickel Cobalt chloride, cobalt sulfate Potassium dichromate Molybdenum Manganese Titanium, titanium oxalate Aluminium Vanadium Zirconium Niobium Tantalum
Bone cement	Polymethyl methacrylate (PMMA) 2-HEMA (2-hydroxyethyl methacrylate) Benzoyl peroxide *N, N*-dimethyl-*para*-toluidine (DMPT) Hydroquinone Liquid bone cement Liquid plus powder bone cement
Antibiotics	Bacitracin Neomycin Gentamycin
Skin glues	Dermabond® and SurgiSeal®: 2-octyl-cyanoacrylate Histoacryl®, Indermil®, GluStitch®, GluSeal®, PeriAcryl®, and LiquiBand®: *N*-2-butyl-cyanoacrylate Epiglu®: ethyl-2-cyanoacrylate

sion (ALVAL) was introduced, which was to correspond to a delayed-type metal hypersensitivity reaction. The above suggestion was based on the results of histological examinations carried out in 19 patients with failed MOM total hip replacements with features of a diffuse, perivascular infiltrate of T cells, B cells, and plasma cells associated with macrophages, a massive fibrin exudate, and areas of necrosis [33]. In another study of 52 revised MOM resurfacing hip arthroplasties the presence of an inflammatory cell infiltrate of macrophages and lymphocytes, containing CD68+/CD14+/HLADR+ macrophages were confirmed. In addition, lymphoid aggregates containing CD3+ T cells and CD20 + B cells were present, which clearly indicated both cytotoxicity and hypersensitivity to metal particles [34].

The gold standard in the diagnosis of an allergic reaction to metal of the implanted prosthesis is an intraoperative biopsy and histopathological examination of the obtained material. The diagnosis of a metal or cement allergy requires a multidisciplinary preparation [35]. The assessment considers the presence of three different lymphocytic infiltration patterns, which may be diffuse with no aggregates in the examined material, may form perivascular aggregates predominantly of T lymphocytes and perivascular aggregates composed of T and B lymphocytes with germinal centres [36].

The dissimilarity and significance of the described lymphocyte infiltration patterns at the site of implant rejection have not been elucidated and a strict relationship with an allergic reaction has not been demonstrated. Fibrous membrane formation is often observed at the site of the implant, even in the absence of a loose implant. Nevertheless, another study involving 25 knee arthroplasty patients showed that fibrous membrane was found in 81% of the patch positive patients with the marked IFN-expression [37].

Obtaining positive results in the metal patch test in patients with an allergic history, especially with the presence of metal dermatitis, is understandable and indicates the existing risk of implant rejection. Patients with positive results of the metal patch test received implants not containing the predefined metal allergens, which resulted in no symptoms of an allergic reaction to metal in any of the patients. At the same time, in the patients with conventional implants, metal allergy occurred in 25% [2]. For the above-mentioned reasons, in order to avoid joint failure and the need for revision surgery, it is advisable to perform preoperative and postoperative allergic diagnostic tests for the most commonly used components (Table 2). In the opinion of dermatologists and allergologists the patch testing is currently the best diagnostic test for metal hypersensitivity reactions [38].

A lack of consensus regarding the utility of pre-implant testing in patients qualified for spine surgery and for hip or knee replacement in patients with a history of metal hypersensitivity creates the risk of a situation where an important issue is overlooked, especially from a humanistic and medico-legal perspective. The facts presented in the analysis clearly indicate the validity of allergological tests in patients with a history of metal hypersensitivity before making a decision to choose the implantable material.

Conclusions

Based on the available analyses, it can be concluded that patients with spinal or orthopaedic implants constitute a group of patients who react to metals, methyl methacrylate, and antibiotics. For this reason, patients qualified for implant surgery should undergo pre-implant testing that includes both the materials and its alternative replacement. In turn, post-implant patients with loosing of prosthesis should undergo patch testing to the implant components to document specific sensitization and help to select alternatives.

There is no practical guide on how to differentiate between metal hypersensitivity and infection in spinal and orthopaedic surgery. However, it must be taken into account that the mechanism for implant loosening may be the result of hypersensitivity and a cytotoxic process in response to prolonged wear of the prosthesis, what can explain the "aseptic" cause of implant failure.

Conflict of interest

The authors declare no conflict of interest.

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