Clinical and diagnostic challenges of metal implant allergy using the example of orthopaedic surgical implants

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Summary

The focus of this review are allergic reactions to orthopaedic-surgical metal implants. The spectrum of metal implant associated potential allergic reactions encompasses eczema, impaired wound and fracture healing, infection-mimicking reactions, effusions, pain and loosening. Nickel, cobalt and chromium seem to be the predominant eliciting allergens. Despite the growing number of respective publications the topic „metal implant allergy" remains a diagnostic challenge. Initially, differential diagnoses should always be excluded in cooperation with surgery collegues. It is recommended to perform a combined evaluation of medical history, clinical findings, patch testing and histology. The lymphocyte transformation test (LTT) can indicate metal sensitization, but it needs careful interpretation. Allergists can provide a substantial contribution to this interdisciplinary topic.

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Key words

Allergy – metal implant – nickel – chromium – cobalt – bone cement – patch test – lymphocyte transformation test

Background

A contact allergy to nickel, cobalt or chromium is frequent not only in the professional environment but also in the general population [1]. However metal exposure takes not only place by skin contact with articles of daily life but also increasingly by metal implants. These include osteosynthesis materials and endoprostheses, as well as stents, heart valve replacements, pacemakers, and implants in ear, nose and throat medicine, gynaecology and dentistry. Metal-allergic reactions can thus appear for example as eczema but also as chronic peri-implant inflammation with pain, effusion or loosening [2, 3]. Given the aging population and the increasing use of metal implants, also an increasing number of allergy-related implant complications are to be expected. In Germany alone in the year 2011 232,320 total hip and 168,486 total knee endoprostheses were implanted – and about 10.4 %

Abbreviations

Co	Cobalt
CoCrMo	Cobalt-chromium-molybdenum
Cr	Chromium
FDA U.S.	Food and Drug Administration
LTT	Lymphocyte transformation test
MHRA	Medicines and Healthcare Products Regulatory Agency
Mo	Molybdenum
M-o-M	Metal-on-metal
PMMA	Polymerized polymethylmethacrylate
RKI	Robert Koch-Institute
SI	Stimulation index

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respectively 9.5 % of these surgeries were complication-related revision surgery [4].

Already more than 30 years ago, cases of osteosynthesis dependent eczema and implant failure have been reported in association with metal allergy. Over the years these seemed to be individual case reports in which the causal link between the clinical picture and diagnosis of allergy remained unclear. While only a few research groups in North America – especially J. Hallab's group – are working on the topic implant allergy, there is some more activity in Europe [5, 6, 7]. The Danish research group around J. Thyssen worked for many years in the field "metal allergy and implants" and has recommended extensive patch testing (including previously not widely evaluated metal preparations) in a review article to clarify intolerance reactions [6]. The orthopedic group led by Donatella Granchi from Bologna gave a critical comment on "metal hypersensitivity testing in patients undergoing joint replacement" based on 22 publications [5]. She points out that in patients with implant failure compared to stable implant more frequently metal allergy is found, but that detection of allergy is not equivalent with "elicitor of implant failure". Accordingly a general pre-or postoperative "allergy screening" is not recommended. In addition, there are patients who tolerate the respective implanted alloy despite the presence of cutaneous metal allergy [8]. Certainly many differential diagnoses have to be considered in arthroplasty-related complications before an allergologic work-up [9]. After all, characteristics of different peri-implant inflammation patterns are increasingly described (in addition to the well known foreign body reaction with, for example, particle-induced inflammasome activation [10]), including the postulated lymphocytic hypersensitivity reaction at the joint [11, 12]. It is not yet proven that the latter is a manifestation of type IV allergy.

Also the "philosophy" of arthroplasty is different [13]: For example in the United States, until recently, often metal-on-metal (MoM; directly coupled) hip replacement was used – in Europe (except England) surgeons were more conservative. In the interdisciplinary statement on metal implant allergy which was published 2008 the main authors Thomas and Thomsen had advised against MoM hip arthroplasty in patients with metal allergy [2], which was accordingly taken critically. In the year 2010 the British Health Agency (MHRA) has put all metal-on-metal bearings under supervision with a "medical device alert" [14]. Meanwhile there is an production stop of two models because of complications and the U.S. Food and Drug Administration (FDA) published in 2013 "Concerns about metal-on-metal hip implants" [15]. However, register data are not only helpful to detect high rates of complications and/or implant loss of certain metal implants (especially endoprostheses). For the first time the Australian arthroplasty register named also "metal sensitivity" as a reason for revision, in fact in about 0.9 % of the revised shoulder endoprostheses and 5.7 % of the revised total hip arthroplasty [16].

As part of our for more than 10 years existing special ambulatory for patients with suspected implant allergy we see on the one hand patients with unusual clinical pictures. The most common constellation however are knee arthroplasty patients with complaints leading to revision without "conventional orthopedic" causes such as infection, malposition or malalignement [9, 17]. In the following we will inform you about implant materials, clinical pictures and allergy diagnostics in suspected implant allergy.

Materials

For endoprostheses usually cobalt-chromium-molybdenum (CoCrMo)- and titanium-alloys are used. Bearing partners are made of polyethylene, ceramic or there is direct M-o-M-pairing (at the hip). As osteosynthesis material stainless steel and usually titanium and its alloys are used. The knee and hip arthroplasty is often (partly) cemented. The bone cements are acrylate-based.

CoCrMo-alloys

The major constituent of these alloys used as standard for the shoulder, hip and knee arthroplasties, is cobalt. The proportions by weight are about 64 % cobalt, 28 % chromium, 6 % molybdenum, and about 0.5 % of nickel [18]. It has been known for a long time that metal ions will be released in the peri-implant tissue but also in the whole organism because of corrosion and wear particles [19]. However, the weight fraction does not reflect the exact percentages of these metals released by corrosion or wear particles [20].

Stainless steel

Applications are stainless steel wires such as "Kirschner-wire", cerclage wires or multifilamentary wires as well as intramedullary nails and osteosynthesis plates and screws. Stainless steel is composed mainly of iron. In addition, it contains approximately 18 % chromium, about 15 % nickel and about 3 % of molybdenum.

Titanium and its alloys

Pure titanium is composed of about 99 % titanium. Very low traces of nickel may be present. An accidental nickel contamination is also possible – but probably rare [21]. Titanium alloys consist mainly of titanium (at least 87 wt %) and are containing additionally either 6 % aluminum and 4 % vanadium, or 6 % aluminum and 7 % niobium.

Bone cements

Bone cements consist of acrylates, which are mixed shortly before use in patients and then harden inside the body. The two reacting components are: methyl methacrylates (liquid component) and already polymerized poly-methylmethacrylate (PMMA) "beads" (powder component). For directing the polymerization additives are present, such as dibenzoyl-peroxide, N,N-dimethyl-p-toluidine and 2-(4-[dimethylamino]-phenyl) ethanol. Other constituents are X-ray contrast agents, stabilizers, colorants (such as copper-chlorophyll-complex) and often antibiotics such as gentamicin [22].

Implant modifications for patients with metal allergy

In the article by Bader et al. [23] common variants are summarized. These are standard (CoCrMo) implants with titanium-based coating, models with "multi-layer" surface coating, oxinium-based surface hardening or endoprostheses based on ceramic. Long-term observations on efficiency and stability are being performed at present so that final evaluation is not yet possible.

Clinical pictures

In the following, we focus on orthopaedic-surgical metal implants. In **Tab. 1**, examples of implant-associated allergic reactions are listed.

Skin reactions

Eczema was observed especially after osteosynthesis of the extremities in association with nickel, chromium or cobalt allergy [2, 24, 25]. In addition to eczema and recurrent erysipelas-like erythema, swelling and impaired wound healing are described [26]. After cerclage with steel wire eczema was observed in patients with sternotomy in association with nickel allergy [27]. In addition erysipelas looking vasculitis-like reactions have been reported [28]. Also remaining metal fragments or particles related to saw/drilling instruments may cause local allergy-related complications. The persistent redness, itching and swelling of the big toe of a nickel-allergic patient is exemplary. Even after removal of the Kirschner wire used after osteotomy, complaints persisted and radiology showed local persistence of saw-wear particles [29]. A nickel-/cobalt-allergic patient showed a massive eczema reaction, and impaired wound healing to a (according to manufacturer's instructions) pure titanium osteosynthesis - however a significant rate of nickel release from the shims and screws used could be demonstrated [21]. Local or generalized eczema in knee or hip replacements are rarely reported [30]. Cutaneous vasculitis-associated hemorrhage is also rarely encountered [31]. Skin lesions (fistula, eczema, local redness) as an expression of bone cement intolerance are possible, but difficult to prove [32]. On the other hand, in case of failure of non-cemented MoM hip arthroplasty, the possible relevance of a metal allergy could be corroborated in conjunction with peri-implant histology [33]. Histological examination of implant-associated cutaneous complications is recommended in order to not overlook rare findings such as reticular erythema [34] or intralymphatic histiocytosis [35].

Table 1

Implant material and possible manifestation of implant allergy (from [26])

Type of implant	Described allergic reaction
Osteosynthesis material	Impaired wound healing, eczema, delayed fracture healing (questionable: pain, urticaria, "pseudoerysipelas", vasculitis)
Kirschner-/stainless steel wire	Impaired wound healing, eczema, sterile osteomyelitis, swelling (questionable: swelling, pain, "pseudoerysipelas")
Hip-/Knee-arthroplasty	eczema, swelling, effusion, loosening, pain (questionable: "pseudoerysipelas", cystic "pseudotumors", arthrofibrosis)
Bone cements	Still in discussion: fistula, pain, effusion, loosening

Other reactions

In connection with metal allergy impaired wound and fracture healing have been described [21]. Especially in knee arthroplasty we have observed recurrent pain, effusion, loosening and reduced range of motion without infection but with associated metal allergy [17]. This also applies to patients with hip arthroplasty. Such cases were interpreted as metal implant allergy in synopsis of proven metal allergy and peri-implant lymphocytic inflammation particularly in patients with MoM pairing. Of course, infection or, for example mechanical causes have to be excluded first. The chain of evidence becomes better if appropriate patients are followed up after revision with "alternative materials" [7, 36]. For a number of situations the role of metal allergy, however, is still to be determined: Aseptic loosening of endoprosthesis with implant-related osteolysis; persistent pain; persistent inguinal pain and cystic "pseudotumor" development after resurfacing with metal-metal bearing; exaggerated periarticular fibrosis ("arthrofibrosis") with restricted range of motion.

Allergological diagnostics in suspected metal implant allergy

Theoretically there may be patients prior to first implantation or persons with complications due to their implant [37].

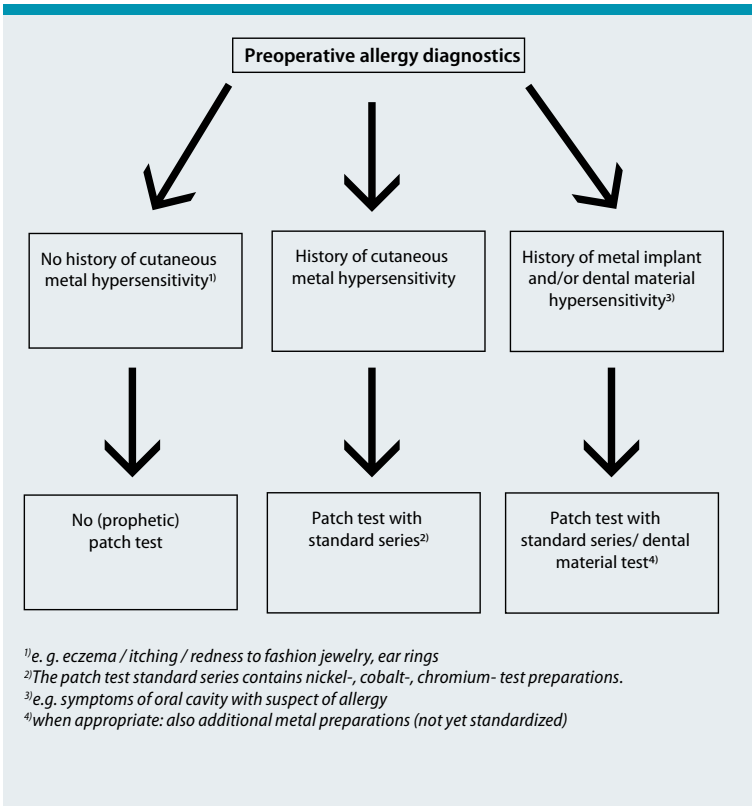

Fig. 1: Preoperative allergy diagnostic (from [37])

"Suspected allergy" before surgery

Preoperative "prophylactic-prophetic" compatibility testing should not be performed. This matches also with the statement in the guideline of patch testing with contact allergens by Schnuch et al. [38]: "the patch test is not suitable, to predict the development of allergic contact dermatitis (in the sense of a 'prophetic testing')". Only when anamnestic indications of previous corresponding intolerance reactions are present, a possible metal allergy or potential allergy to bone cement components can be clarified. **Fig. 1** summarizes this strategy. The review article by Geier et al. [39] stresses – and this is still valid – that there is no consensus recommendation for patch test details in suspected implant intolerance.

Suspicion of metal implant allergy

After exclusion of the most frequent differential diagnoses (such as infection) by the supervising orthopedic surgeon, but also by the dermatologist (psoriasis?, tinea?, alternative contact allergy triggers?) the patch test is performed. The histology of peri-implant tissue can give an additional indication of a hypersensitivity reaction by lymphocyte dominated inflammation. A T-cellular metal sensitivity can also be questioned by the lymphocyte transformation test (LTT). This is however still restricted to scientific laboratories which evaluate the results critically case by case for the clinical relevance [2]. **Fig. 2** suggests the appropriate diagnostic steps.

Allergological medical history

In addition to indications of a potential metal allergy (redness, itching, eczema to jeans button, to fashion jewelry or intolerance of leather goods) also a local intolerance to dental resins or artificial acrylate-based finger nails could be hints to possible contact allergy to acrylates and additives such as benzoyl peroxide (and a corresponding testing be justified).

Patch testing

The standard series covers with nickel, chromium and cobalt preparations essential implant components. There is still no official consensus in relation to bone cement testing. Thus, only the author's approach is given here: in our ambulatory the following substances are tested as they are available from other test series: "gentamicin sulfate, benzoyl peroxide, hydroquinone, 2-hydroxyethylmethacrylate, copper-(II)-sulfate, methylmethacrylate, N, N-dimethyl-p-toluidine". We recommend also a delayed reading after six or seven days, as we often observe late reactions to gentamicin. Additional metal preparations are available, but not yet standardized – and their use should be critically decided case by case [33]. The clinical relevance of test results must, as always, be interpreted in the context of additional informations.

Histology

For diagnosis of endoprosthesis loosening or for histopathological classification of the reaction pattern in periprosthetic membranes a consensus classification exists [40]. A definition of metal allergy-induced peri-implant reaction pattern is currently being developed, and the author is cooperating in this matter with the reference pathologist of allergy research group of the German orthopedic and surgery society. In combination with the consensus classification of peri-implant membrane the analysis of the local cytokine pattern further adds to develop tools for evaluation of peri-implant lymphocytic inflammation [12].

Lymphocyte transformation test (LTT)

This rather scientific test normally uses the antigen-induced proliferative response in relation to the baseline proliferation of unstimulated cultures (stimulation index [SI]) as measurement parameter.

We have – as well as other laboratory groups – set the indication-limit for sensitization on SI > 3 [41] and give interpretation only in conjunction with other diagnostic parameters. Only with the restriction of critical evaluation, the LTT can be used as a complementary method for example when investigating a suspected allergic drug reaction [42]. It must be carefully assessed whether the found sensitization also means disease-causing hypersensitivity [43, 44]. Even for nickel allergy quality assessments of LTT procedures are very rare [45]. Accordingly, the Robert Koch Institute (RKI) [43], did not publish a general recommendation for the LTT. On the other hand future development steps (example: comparative study with symptom-free arthroplasty patients [30]) and a follow-up study with evaluation of the clinical relevance of LTT result can lead to LTT optimization.

Conclusion

The diagnosis "implant allergy" results from the synopsis of as many diagnostic steps as possible. This includes medical history, clinical findings, patch testing and analysis of peri-implant tissue – with patch testing and histology appearing essential to us. The LTT gives supplementary information, but requires a thoughtful interpretation. It is encouraging that allergists can very well provide an important contribution to this interdisciplinary topic.

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Conflict of interest
The author indicates no conflict of interests.

Annotation
Prof. Dr. Peter Thomas was appointed as reference allergist by the German Orthopaedic Society as well as by the German Society of Dental Implantology.

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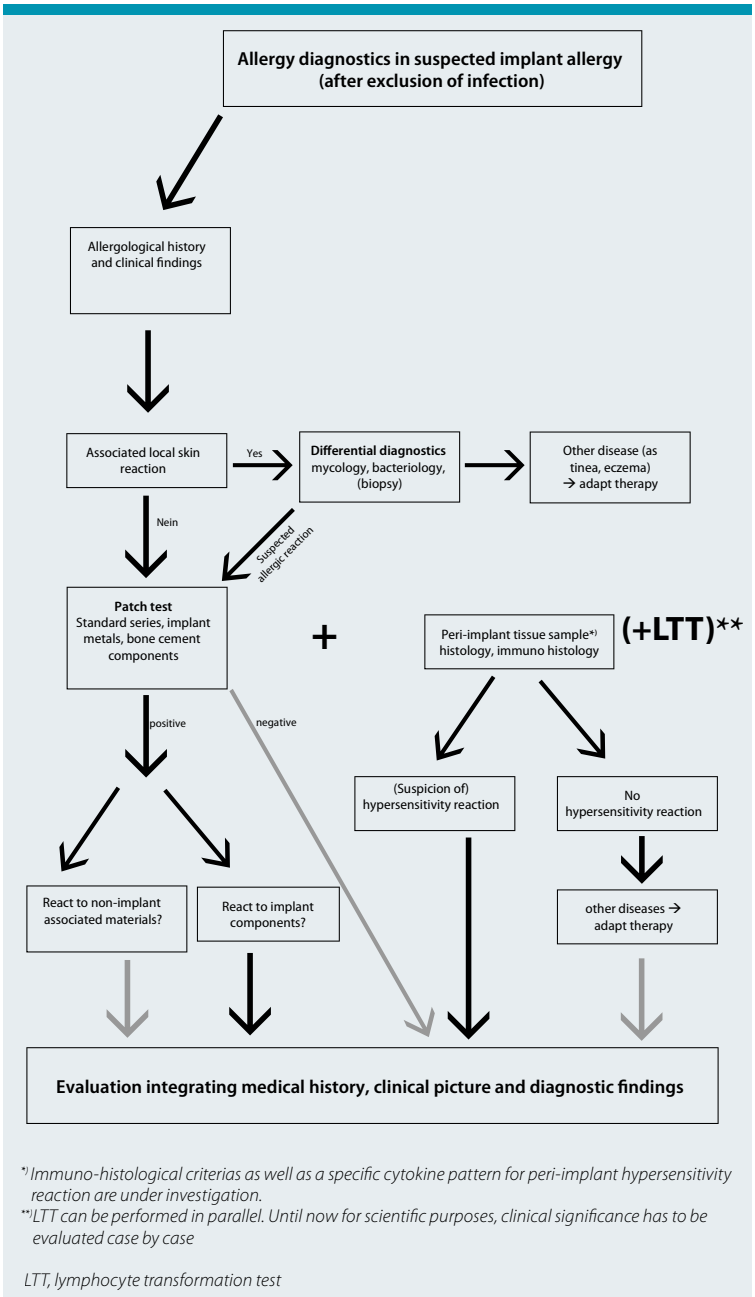

Fig. 2: Diagnostic in suspected metal implant allergy (from [37])

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