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

Peter Thomas
Department of Dermatology and Allergology, Ludwig-Maximilians-University Munich, Germany

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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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% form 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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Metall implant allergy

review article

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

Already more than 30 years ago, cases of osteo-
synthesis 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 exten-
sive 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 test-
ing 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 de-
tection of allergy is not equivalent with “elicitor of
implant failure”. Accordingly a general pre- or post-
operative “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 differ-
ential diagnoses have to be considered in arthro-
plasty-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
inflammamomase activation [10]), including the pos-
tulated 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 interdisci-
plinary 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 accord-
ingly taken critically. In the year 2010 the British
Health Agency (MHRA) has put all metal-on-met-
al bearings under supervision with a “medical de-
vice 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 spe-
cial 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 com-
plaints leading to revision without “conventional or-
thopedic” causes such as infection, malposition or
malalignment [9, 17]. In the following we will in-
form you about implant materials, clinical pictures
and allergy diagnostics in suspected implant allergy.

Materials

For endoprostheses usually cobalt-chromium-mo-
lybdenum (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 stand-
ard 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 be-
cause of corrosion and wear particles [19]. However,
the weight fraction does not reflect the exact per-
centages 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 osteosyn-
thesis plates and screws. Stainless steel is composed
mainly of iron. In addition, it contains approxi-
mately 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 acci-
dental 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-methylenacrylate (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].

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].

| 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 |
“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.

Prof. Dr. Peter Thomas
Department of Dermatology and Allergology
Ludwig-Maximilians-University Munich
Frauenlobstraße 9–11
80337 Munich, Germany
E-Mail: peter.thomas@med.uni-muenchen.de

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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