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Title: Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery

Review article

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What's already known about this topic?

It is known that insertion of orthopaedic implants may release metal ions and sensitize or elicit an allergic immune response. It is unknown whether the risk of allergic complications following insertion of metallic orthopaedic implants may be increased in previously metal sensitized individuals.

What does this study add?

This review updates the reader on the absence of scientific evidence for performing patch testing prior to orthopaedic surgery. Also, it suggests diagnostic criteria for the clinical work-up of patients suspected with allergic reactions following implants surgery.

ABSTRACT

Allergic complications following insertion of metallic orthopaedic implants, include allergic dermatitis reactions but also extra-cutaneous complications. Since metal allergic patients and/or surgeons may ask dermatologists and allergologists for advice prior to planned orthopaedic implant surgery, and since surgeons may refer patients with complications following total joint arthroplasty for diagnostic work-up, there is a continuous need for updated guidelines. This review presents published evidence for patch testing prior to surgery and propose tentative diagnostic criteria which clinicians can rely on in the work-up of patients with putative allergic complications following surgery. Few studies have investigated whether subjects with metal contact allergy have increased risk of developing complications following orthopaedic implant insertion.

Metal allergy might in a minority increase the risk of complications caused by a delayed type hypersensitivity reaction. At present, we do not know how to identify the subgroups of metal contact allergic patients with a potentially increased risk of complications following insertion of a metal implant. We recommend that clinicians should refrain from routine patch testing prior to surgery unless the patient has already had implant surgery with complications suspected to be allergic or bare a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or a health provider. The clinical work-up of a patient suspected of having an allergic reaction to a metal implant should include patch testing and possibly in vitro testing. We propose diagnostic criteria for allergic dermatitis reactions as well as non-eczematous complications caused by metal implants.

People suffer from bone and joint conditions worldwide. Surgery of the affected area may involve insertion of implants, e.g. joint replacement or internal fixation of bone fractures. Metallic implants are frequently made of stainless steel, vitallium, titanium, zirconium and cobalt-chromium-molybdenum alloys. These are typically composed of metals such as aluminum, chromium, cobalt, nickel, molybdenum, vanadium, titanium, and iron ¹. Allergic complications following insertion of metallic orthopaedic implants, reported since the 1960's, include localized allergic dermatitis, urticaria, bullous reactions, vasculitis and impaired wound healing overlying the metallic implants ²; systemic allergic dermatitis reactions at more distant anatomical sites ³⁻⁵; but also extra-cutaneous complications such as implant loosening, pain, swelling and chronic inflammation (which are all conditions with many other aetiologies than metal allergy) ⁶⁻⁹. Metals corrode in vivo, and release metal ions (depending on the alloy) that may afterwards bind to proteins and activate the immune system locally and in remote organs following haematogenous transport. It is generally accepted that skin eruptions are explained by a delayed type hypersensitivity response effectuated by T-lymphocytes whereas the pathogenesis of extra-cutaneous allergic complications, e.g. total joint arthroplasty implant failure, seems to be much more diverse and complicated.

Today, the overall risk of developing extra-cutaneous allergic reactions following total hip arthroplasty is comparable in metal patch test positive and negative subjects ¹⁰. However, since second generation metal-on-metal hip prostheses have regained popularity, this area has recently received increasing attention ¹¹. Prevalent non-allergic causes of total joint arthroplasty failure include aseptic osteolysis, infection, recurrent dislocation, and fractures ¹². Debris induced immune reactivity, including delayed type hypersensitivity reactions to metals, have been suggested to cause up to 5% of total joint arthroplasty failure 7 years after surgery ¹³. Large particulate wear debris particles (more than 150 nm to 10 µm) are phagocytosed by cells including macrophages, which may then present antigens to circulating T-lymphocytes resulting in delayed type hypersensitivity reactions ¹³. Hallab et al., found a linear correlation between serum metal ion levels and lymphocyte reactivity suggesting that in vivo metal release is directly associated with metal contact allergy ¹⁴. Furthermore, stimulated T-cells may generate pro-osteoclastogenic factors that can alter bone homeostasis ¹⁵. The histological feature of the rarely observed aseptic lymphocyte dominated vasculitis-associated lesions (ALVAL) has been suggested to represent a systemic T-lymphocyte-

mediated delayed type hypersensitivity reaction^{8,9}. Thomas et al., supported this notion as the frequency of metal patch test positivity was higher in 16 patients with revised metal-on-metal arthroplasty than in controls¹⁶. Infrequent locally destructive pseudotumours have been reported in mainly women with metal-on-metal resurfaced hips¹⁷. Despite the exact aetiology has not been established, pseudotumours appear not to be dominated by delayed type hypersensitivity reactions¹⁸. In general favour of a Th1-driven allergic immune response to metallic hip implants, Hallab et al., found elevated production of interferon (IFN)- γ to metals in metal reactive hip arthroplasty patients when compared to controls¹⁹. Thomas et al., showed a Th1 driven immune response with expression of IFN- γ and IL-6 in peri-implant tissue from a chromium allergic patient with intolerance to an orthopaedic cobalt-chromium alloy²⁰. Summer et al., showed that patients with complicated total joint arthroplasty (knee or hip) and concomitant nickel patch test reactivity had a strong interleukin (IL)-17 response but virtually no IFN- γ expression whereas symptom free arthroplasty patients with nickel patch test reactivity had moderate IFN- γ expression but no IL-17 production²¹.

It is important to emphasize the difference between metal contact allergy (sensitization) and allergic metal dermatitis (elicitation of a disease state)²². Thus, contact allergy is an asymptomatic condition defined by immunological alertness in an individual following repeated or prolonged skin contact with a given allergen (or perhaps following insertion of an implant). Re-exposure to the allergen at the skin surface in sufficient concentrations will in most cases result in allergic contact dermatitis, the elicitation phase defined by dermatitis reactions (or perhaps by implant failure). Thus, a person can be contact allergic (defined by a positive patch test reaction to the allergen) without knowing it and without ever having experienced any signs or symptoms such as redness, itch or dermatitis. In line with this, dermatologists sometimes find it difficult to establish relevance of positive patch test reactions. This can be due to 1) patient recall bias, 2) cross-reactivity to an allergen that has not been included in the test battery, 3) or simply that the patient has been sensitized but never experienced dermatitis following exposure.

Since metal allergic patients and/or surgeons may ask dermatologists and allergologists for advice prior to planned orthopaedic implant surgery, and since surgeons may refer patients with complications following total joint arthroplasty for diagnostic work-up, we propose tentative diagnostic criteria that clinicians can rely on and to aid researchers on causality. Merle et al. published diagnostic

criteria in 1992²³; however, we believe an re-evaluation is necessary due to subsequent developments in medicine. We have not addressed the issue of contact allergy to cement haptens and other non-metallic constituents, as intolerance to these substances is generally infrequent. Also, we have not addressed allergic complications following dental and cardiac implants as we believe that pathomechanisms to some degree may be different²⁴. However, the rationale behind the proposed diagnostic criteria may to some degree also be applied for non-metallic allergens and non-orthopaedic metallic implants. A systematic review was recently performed²⁵; hence this review rather attempts to make a practical and clinical approach to this difficult subject. A literature search in Pubmed-Medline was performed using the following search terms: metal allergy, sensitivity, sensitization, delayed type hypersensitivity, patch test, nickel, cobalt, chromium, titanium, knee, hip, arthroplasty, surgery, complications, loosening, pain, ALVAL, pseudotumour, and orthopaedic.

Two situations may occur:

- 1. A patient is referred for advice before implantation. What should you consider?*

Previous findings

It remains controversial whether subjects with metal allergy are at increased risk of developing complications following insertion of metallic orthopaedic devices or whether implant loosening result in a higher incidence of metal allergy²⁶. This dilemma is a general health problem of potentially growing significance considering the rapidly ageing populations in Western Europe and the US²⁷. Merritt et al., showed that subjects may develop metal contact allergy (as defined by a positive leukocyte migration inhibition test) following total joint replacement; a finding that underscores the sensitizing potential of implants²⁸. However, Swiontkowski et al., showed that the conversion from negative to positive metal patch test reactivity before and after trauma implant surgery more or less equalled conversion from positive to negative metal patch test reactivity²⁹. Hallab et al., showed that the prevalence of metal allergy was 25% among patients with well-functioning hip arthroplasties and 60% among patients with a failed or a poorly

functioning implants ⁷; considerably higher frequencies than general population estimates ^{30;31}. Higher metal contact allergy prevalences have also been shown in patients with total knee arthroplasty when compared to general population estimates ^{32;33}. Despite these observations, the higher frequency of metal contact allergy in patients with metallic orthopaedic implants might rather be explained by primary implant loosening resulting in secondary sensitisation than vice versa. Niki et al., performing modified lymphocyte stimulation test in 92 patients prior to total knee arthroplasty ³⁴, remarkably showed that 24 patients were lymphocyte stimulated to at least one metal prior to surgery and that 5 of these developed metal-related dermatitis (2 had generalized dermatitis and 3 had localized dermatitis). In 2 patients, revision surgery resulted in dermatitis clearing and furthermore negative lymphocyte stimulation test outcome. Reed et al., patch tested 21 patients prior to insertion of an orthopaedic implant and showed that 5 had metal contact allergy towards a metal used in the implant planned for insertion ³⁵. The surgeon utilized a different implant in 4 of these patients. In the 5th patient, the surgeon disregarded a positive patch test reaction to nickel since the implant was made of stainless steel ³⁵. A Danish case-control study including 356 patch tested dermatitis patients found no increased risk of implant failure in metal allergic patients after 1-12 years follow-up ¹⁰. Carlsson and Möller, followed 18 patients with contact allergy to chromium, cobalt and/or nickel for a mean of 6.3 years (after insertion of a metallic device containing one of these allergens) and found no dermatological or orthopaedic complications ³⁶. Carlsson et al., also showed that 3 of 112 patients undergoing total hip arthroplasty developed metal allergy (2 developed cobalt allergy and one developed nickel allergy) ³⁷. Of interest, one study showed that patch test reactivity to bone cement haptens and a medical history of hypersensitivity prior to hip surgery negatively influenced total hip replacement ³⁸. However, patch test reactivity to metals did not influence total hip replacement.

Considerations

Overall, few studies investigated whether subjects with metal contact allergy have increased risk of developing complications following orthopaedic implant insertion. When interpreting study outcomes, remember that the selection of studies is heterogeneous covering different implants (arthroplasties, bone-lengtheners, nails and pins) made of different alloys. Furthermore, most studies

included relatively few patients allowing room for random error. Also, follow-up time cannot be considered sufficient in all studies. It remains unknown whether the same pathogenic mechanisms cover e.g. loosening of total hip arthroplasties and allergic dermatitis reactions overlying an implant. Finally, a large proportion of metal sensitivity observed following implantation is caused by nickel^{18;32;38}. In some patients, nickel allergy is caused by excessive nickel exposure following skin contact with consumer items rather than by nickel exposure from the implant itself. In addition, it has been speculated whether the high incidence of nickel allergy could be a proxy for an overall increased immune response^{18;38}. Also, some studies demonstrated high *de novo* incidences of sensitization to metals that are not contained in the implants making the relevance of these allergies doubtful³². However, it should be underscored that allergic reactions also have been related to chromium and cobalt^{16;39}; contact allergies that are uncommon in the general population (0-1%)³¹ making patch test positive reaction likely to be caused by the implant. There seems to be little doubt that metal allergy in a few subjects increase the risk of complications caused by a delayed type hypersensitivity reaction and that replacement with implants made of different alloys (e.g. titanium) may be a successful approach⁴⁰.

Based on the complex findings, it is difficult to make general principles for good clinical practice prior to surgery. Complications caused by delayed type hypersensitivity reactions to metal ions are rare and at the same time nickel allergy remains frequent in the general population³¹ and nickel, cobalt and chromium allergy remains frequent in dermatitis patients^{41;42}. This obviously makes it difficult to identify the few allergic subjects at risk of developing implant failure. Large-scale routine screening for metal allergy prior to surgery is therefore not recommended as it requires large resources and since the only logical consequence of such an initiative would be to not to insert implants that contain the offending metal(s) in allergic subjects. It may be tempting to increase the use of titanium alloys as titanium allergy is infrequent; however, such an approach will increase health care costs considerably and may not be necessary in most patients. Overall, it seems relatively straightforward to advise patients with negative patch test reactions prior to surgery whereas it is more troublesome in patients with positive patch test reactions as clinical relevance determination is difficult. At present, we do not know how to identify the subgroups of metal contact allergic patients with a potentially increased risk of complications following insertion of a metal implant. Perhaps, risk assessment might be based on the presence or absence of IL-17 in the future²¹. We recommend that

clinicians should refrain from routine patch testing prior to surgery unless the patient has already had implant surgery with complications suspected to be allergic or bare a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or a health provider. In such cases, it is advisable to avoid implants containing metals that the patient has reacted to during allergy testing (table 1). Knowing the type of implant a patient will be receiving is important for the diagnostic assessment of metal reactivity. It may be useful to do allergy testing with custom made metal discs with a composition similar to the implant(s) planned for insertion. Recently, Beecker et al., proposed a novel technique using subcutaneous metal implants to predict complications following knee implant surgery ⁴³. Bruze recently emphasized the differences within and between countries in the advice and management of such patients ⁴⁴. He suggested that the differences, at least the international ones, could be partly explained by differences in legislation rather than by differences in the interpretation of the available medical information. For example, in the United States, patients with orthopaedic implants seem to be more frequently evaluated for allergy compared with Sweden and Denmark, where virtually no such patients are evaluated ⁴⁴.

2. *A patient is referred after surgery with dermatitis overlying the implant or with implant failure.*

What should you consider?

Previous findings

There is evidence that complications following implant insertion may be caused by delayed type hypersensitivity reactions to a metal contained in the implant. This was lately illustrated by a 12-year old child that developed systemic allergic dermatitis to nickel and cobalt 3 months after insertion of a metallic plate in a fractured leg ⁴⁵. Removal of the cobalt and nickel containing implant resulted in rapid dermatitis clearing. Another case report described a woman with ALVAL following insertion of cobalt containing hip bearings. The patient was cobalt allergic and all symptoms disappeared rapidly after cobalt implant removal ⁸. The medical literature contains similar case reports and series that have documented the benefits of a diagnostic work-up including allergy testing and removal of offending implants. This also

includes titanium, a metal that most patients generally tolerate well although titanium allergy has been reported ^{46;47}.

Considerations

The clinical work-up of a patient suspected of having an allergic reaction to a metal implant should include patch testing and possibly in vitro testing. Access to in vitro testing may not be available for many allergists and dermatologists and is generally restricted to university clinics. In vitro proliferation testing of metals typically involves measuring the proliferative response of lymphocytes obtained from peripheral blood by routine blood draw and 7-day incubation of peripheral blood mononuclear cells with metals ¹³. The lymphocyte transformation test (LTT) measures the ratio of lymphocyte proliferation after antigen challenge to lymphocyte proliferation in the absence of antigen; referred to as the stimulation index (SI) ⁴⁸. It is sometimes argued that patch testing is insufficient in orthopaedic practice ^{13;29;39;48}, as immune reactivity may be different in the skin and around an implant owing to different antigen presenting cells ³⁹. However, patch testing remains a standardized diagnostic method with low costs whereas in vitro tests are expensive and need to be performed in qualified laboratories. Also, the toxicity of some metals may hamper their in vitro testing, and patch testing may allow screening for more metals ³². However, since in vitro tests may be useful in doubtful cases and offer quantitative estimates their use should be considered. The value of a medical history focusing on previous dermatitis reactions to e.g. jewellery remains unsettled but may be helpful ¹⁶. It has been shown that 2+ and 3+ patch test reactions to metals contained in the offending implant are more strongly associated with complications than 1+ reactions ^{32;38}. No one has made large studies using dilution series patch testing. It is possible that metal allergic patients with complications caused by delayed type hypersensitivity have a lower reactivity threshold. We propose diagnostic criteria for allergic dermatitis reactions as well as non-eczematous complications caused by metal implants (table 2 and 3). It should be underscored that metal patch testing does not always result in a diagnosis despite clinical suspicion of an allergic aetiology. Thus, Reed et al. patch tested 22 patients with different complications after insertion of an orthopaedic or cardiac implant and found no positive reactions to relevant metal allergens ³⁵. If the

dermatologist or allergist can support a causative association, removal of the offending implant should be considered.

General remarks

This review attempts to propose diagnostic criteria for the dermatological work-up of patients receiving orthopaedic implants and for patients with complications following orthopaedic implant surgery. The criteria are based on reason, logic and scientific evidence and may have flaws. However, there is a clear need for such criteria that clinicians can depend on. We have not addressed the importance of implant materials; an area that should be further explored to understand corrosion, endurance and safety of implants. We are likely to learn much more about this complicated area of allergy and dermatology in the future and we recommend that dermatologists participate in the difficult debate on allergy work-up of such patients. Additional prospective studies including these criteria should help clarify the relationship between metal patch test reactivity and clinical cutaneous and extra-cutaneous disease related to implants (table 4). We welcome forming national/international study groups for the discussion and study of this issue, until all patient related issues are clarified.

Table 1. Proposed metals that should be considered for patch testing in patients undergoing evaluation for metal allergy prior to an orthopaedic implant or for metal implant failure. The patch test battery should always reflect the metals currently used in orthopaedic implants and should be continuously updated.

Cobalt chloride 1% pet.
Nickel sulfate 5% (or 2.5%) pet.
Chromium trichloride 2% pet.
Potassium dichromate 0.5% (or 0.25%) pet.
Gold sodium thiosulfate 0.5% pet.
Titanium powder 1% pet.
Vanadium trichloride 2% pet.
Zirconium (IV) oxide 0.1% pet.

Custom made disc made of alloys considered for implantation.

(Copper sulphate 2% pet.)
(Ferric chloride 2 or 5% in pet.)⁴⁹
(Aluminium chloride hexahydrate 10 % in pet.)⁵⁰
(Sodium tetrachloropalladate 3% in pet.)⁵¹
(Manganese chloride 2% aq.)
(Tantalum powder 1% pet.)
(Iridium chloride 1% aq.)
(Indium sulfate 10% aq.)

Allergens marked with brackets are considered of secondary priority for the diagnostic work-up.

Table 2. Objective criteria that support a causative association between metal release from an orthopaedic implant, metal allergy and current allergic metal dermatitis overlying the implant:

1. Chronic dermatitis beginning weeks to months after metallic implantation.
2. Eruption overlying the metal implant.
3. Morphology consistent with dermatitis (erythema, induration, papules, vesicles).
4. In rare instances, systemic allergic dermatitis reaction (characterized by universal dermatitis reactions, typically localized in body flexures).
5. Histology consistent with allergic contact dermatitis.
6. Positive patch test reaction to a metal used in the implant (often strong reactions).
7. Serial dilution patch testing give positive reactions to low concentrations of the metal under suspicion.
8. Positive in vitro test to metals, e.g. the lymphocyte transformation test.
9. Dermatitis reaction is therapy resistant.
10. Complete recovery following removal of the offending implant.

Table 3. Objective criteria that support a causative association between metal release from the implant, metal allergy and delayed type hypersensitivity reactions such as implant loosening, malfunction, pain or chronic inflammation.

1. Histology consistent with a delayed type hypersensitivity reaction.
2. Positive patch test reaction to a metal used in the implant (often strong reactions).
3. Positive in vitro test to metals, e.g. the lymphocyte transformation test.
4. Complete recovery following removal of the offending implant material.

Table 4. Future research topics.

1. Removal of implants that have resulted in dermatitis or device failure and analysis for unusual corrosion.
2. Histological examination of peri-implant tissue in patients with complications (patch test positive vs patch test negative).
3. Dilution patch test series for metal allergy in implanted patients with and without complications.
4. Correlation between metal allergy and metal ion concentrations in the blood and urine.

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