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Review article

Allergies in orthopaedic and trauma surgery



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ABSTRACT

Hypersensitivity reactions to implants in orthopaedic and trauma surgery are a rare but devastating complication. They are considered as a delayed-type of hypersensitivity reaction (type IV), characterized by an antigen activation of sensitized T-lymphocytes releasing various cytokines and may result in osteoclast activation and bone resorption. Potential haptens are originated from metal alloys or bone-cement. A meta-analysis has confirmed a higher probability of developing a metal hypersensitivity postoperatively and noted a greater risk of failed replacements compared to stable implants. Hypersensitivity to implants may present with a variety of symptoms such as pain, joint effusion, delayed wound/bone healing, persistent secretion, allergic dermatitis (localized or systemic), clicking noises, loss of joint function, instability and failure of the implant. Various diagnostic options have been offered, including patch testing, metal alloy patch testing, histology, lymphocyte transformation test (LTT), memory lymphocyte immunostimulation assay (MELISA), leukocyte migration inhibition test (LIF) and lymphocyte activation test (LAT). No significant differences between in vivo and in vitro methods have been found. Due to unconvincing evidence for screening methods, predictive tests are not recommended for routine performance. Infectious aetiology always needs to be excluded. As there is a lack of evidence on large-scale studies with regards to the optimal treatment option, management currently relies on individual case-by-case decisions. Several options for patients with (suspected) metal-related hypersensitivity exist and may include materials based on ceramic, titanium or oxinium or modified surfaces. Promising results have been reported, but long-term experience is lacking. More large-scaled studies are needed in this context. In patients with bone-cement hypersensitivity, the component suspected for hypersensitivity should be avoided. The development of (predictive) biomarkers is considered as a major contribution for the future.

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1. Introduction

Total joint replacement is the standard treatment of care for end-stage osteoarthritis and is known for excellent clinical results. In general, materials implanted are well tolerated by the body. However, the host response to implants in orthopaedic and trauma surgery is essential for their clinical performance.

Hypersensitivity reactions in general are known as a state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign agent. Hypersensitivity can be classified as an immediate humoral response driven by antibodies or antibody-antigen complexes or as a delayed cell-mediated response. Implant-associated hypersensitivity reactions are considered as a delayed-type of hypersensitivity (type IV) reaction

and are characterized by activation of sensitized T-lymphocytes releasing various cytokines which results in the recruitment and activation of macrophages. A variety of inflammatory mediators may be involved, such as cytokines (IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IFN γ , IP10), chemokines (MIP-1 α and MIP-1 β) and growth factors (GM-CSF and PDGF). Although the exact pathways remain unclear at present, the common endpoint is osteoclast activation and bone resorption, leading to destabilization of the implant and may even result in revision surgery due to aseptic loosening. Implant loosening caused by hypersensitivity has first been presented in the mid 1970s. Increased attention has been given to high failure rates in second-generation metal-on-metal hip replacements.

Implants currently available in orthopaedic and trauma surgery are made of various materials and may contain stainless steel, cobalt-chromium-molybdenum alloys, nickel, titanium, Vitallium, beryllium, vanadium and tantalum as well as plastic and ceramic components. Released metal components in periprosthetic tissue

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have been reported to exist in different forms, including wear debris, metallo-protein complexes, metal ions in solution and/or by-products of synergistic corrosion and wear processes. Potential haptens causing implant-related hypersensitivity are also known to be originated from bone-cement.

Various terms have been used to describe periprosthetic tissue reactions. Characteristic alterations may include vasculitis with diffuse and/or perivascular lymphocytic infiltration, high endothelium venules, recurrent localized bleeding and/or necrosis. In general, tissue reactions are described according to their predominant cellular response as either (i) macrophage-dominated type without immunological memory, which is mostly seen in foreign-body type reactions, or as (ii) lymphocyte-dominated type of tissue response, describing a T-cell mediated reaction, comprising diffuse and perivascular lymphocytic infiltrates and characterized by an adaptive, immunological memory. The authors prefer the semi-quantitative score proposed by Willert et al. to evaluate histological features and the dominant type of tissue response [1]. We demonstrated in one of our previous studies that the combined surface area comprising number and size of all particles, named as “biologically active area” rather than the size or number of particles alone predicts the type of tissue response [2].

2. Do implant-related allergies exist?

Several study groups aimed to investigate the cause-and-effect relationship between hypersensitivity reactions and implant failure in orthopaedic and trauma surgery. Recently, a systematic review and meta-analysis by Granchi et al. comprising 3634 patients has combined the results of the current literature showing that the prevalence of hypersensitivity was influenced by the following factors: presence and status of the implant, the type of coupling, and the number of haptens tested. According to these authors, metal sensitization manifests more often in patients undergoing joint replacement when compared to the normal population (odds ratio (OR) 1.52 (95% confidence interval [CI] 1.06 to 2.31). The probability of hypersensitivity was higher in particular in patients with failed implants compared to those with stable joint replacements (OR 2.76 [95% CI 1.14 to 6.70]) [3]. Based on seven reports, the average prevalence of metal hypersensitivity (nickel, cobalt or chromium) was compared among the normal population (approximately 10–15%), patients with a well functioning implant (25%) and patients with a poorly functioning implant (60%) [4]. However, these numbers should be interpreted carefully, since it was recently shown that the proportion of positive tests is almost twice compared to that four decades ago. This finding has been interpreted as a consequence of the increased number of haptens tested [3].

The risk for hypersensitivity is thought to be largely depending on the individual's exposure and risk factors including age, gender (female > male), occupation and a positive history of metal hypersensitivity have been reported [5].

Hypersensitivity reactions to implants may present with a variety of symptoms such as pain, joint effusion, delayed wound/bone healing, persistent secretion, allergic dermatitis (localized or systemic), clicking noises, loss of joint function, implant instability and failure. Symptoms mainly exhibit within the first postoperative year after primary implantation. Radiologic findings are typically non-specific and may include radiolucent lines and progressive osteolysis without any bone atrophy. The presence of pseudotumors has been reported in literature.

Objective criteria supporting a causative association between implant-related metal ions and metal hypersensitivity have been proposed by Thyssen et al. including “(i) chronic dermatitis beginning weeks to months after metallic implantation, (ii) eruption

overlying the metal implant, (iii) morphology consistent with dermatitis (erythema, induration, papules, vesicles), (iv) in rare instances, systemic allergic dermatitis reactions (characterized by universal dermatitis reactions, typically localized in body flexures), (v) histology consistent with allergic contact dermatitis, (vi) positive patch test reaction to a metal used in the implant (often strong reaction), (vii) serial dilution patch testing give positive reactions to low concentrations of the metal under suspicion, (viii) positive in vitro test to metals, (ix) dermatitis reaction is therapy resistant and (x) complete recovery following removal of the offending implant” [6].

Though joint registers become more and more established nowadays, reliable epidemiologic data on implant-related hypersensitivity are still lacking; often hypersensitivity-related complications are not systematically collected. In Germany, there is an increasing attempt to overcome this lack of information. Under the supervision of the German reference dermatologist for orthopaedic and trauma surgery, an implant hypersensitivity registry collecting detailed patients' characteristics and documenting the long-term results after revision surgery for implant-related hypersensitivity has been initiated.

In conclusion, given the clinical and temporal evidence, the authors support the theory of hypersensitivity-related complications in orthopaedic and trauma surgery. However, the underlying mechanisms still remain to be fully elucidated. The prevalence presented is inconsistent, and due to diagnostic difficulties, the reported numbers may be not realistic. Because of potential serious clinical implications for the patient, hypersensitivity following implantation of a foreign-body is considered as an important topic for the surgical community.

3. How to diagnose hypersensitivity to implants?

The diagnosis of implant-related hypersensitivity in orthopaedic and trauma surgery is challenging. Although various diagnostic algorithms have been proposed, there is no generally established guideline so far. An overview of in vivo and in vitro diagnostic options for metal hypersensitivity including their objectives and potential drawbacks are given in Table 1.

Patch testing, though controversial, is still the most commonly used diagnostic method and remains considered as gold standard for in vivo assessment. However, it has to be noticed that the FDA approved thin-layer rapid use epicutaneous patch test (TRUE test; Mekos Laboratories A/S Hillerød, Denmark) only contains the most common sensitizers, namely nickel, cobalt and chromium [7]. It does not include the whole variety of antigens relevant for hypersensitivity in orthopaedic and trauma surgery. Extending the patch test to other known triggering substances should be considered, but may lack validation. Critics point out differences in epicutaneous environment compared to deep tissue layers. Antigen-presenting mechanisms may be therefore of limited reflection. Moreover, the actual form of released metal components may not reflect the preparations used in the patch testing panels and be unable to penetrate the skin [8].

Due to the lack of additional benefits through metal alloy disk patch testing, this modified patch testing has not been recommended by the German contact allergy group (Deutsche Kontaktallergie Gruppe, DKG) [9]. For the patient reported history of allergy, a sensitivity of 85.5% and a specificity of 83.5% have been reported in a prospective study by Frigerio et al. [10], and is therefore considered inferior compared to the standard patch test. Evaluating histological features requires an invasive action, but provides the opportunity of investigating the true periprosthetic tissue response. Formalin fixation of tissue samples is required. In

Table 1

Overview of diagnostic options for hypersensitivity reactions in orthopaedic and trauma surgery.

Diagnostic options for hypersensitivity reactions in orthopaedic and trauma surgery		
Test	Objectives	Areas of concern
<i>In vivo</i>		
Patient's history	History of known allergies	Time consuming Relies on patient-reported information
Patch testing	Cutaneous reactions to metal salt preparations	Results may be inconclusive: irritable skin vs true hypersensitivity Variable results after various reading times May induce sensitization Different haptenic potential of relevant antigens in periprosthetic tissue compared to dermal contact
Metal alloy disc patch testing	Cutaneous reactions to metal alloys	Results may be inconclusive: cutaneous pressure effect vs true hypersensitivity Test results are non-attributable to specific metal components Different haptenic potential of relevant antigens in periprosthetic tissue compared to dermal contact May induce sensitization
Histology	True periprosthetic tissue reaction	Invasive Reading is subjective Time consuming Different scoring systems exist
<i>In vitro</i>		
Lymphocyte transformation test (LTT)	Proliferative response of activated lymphocytes	Limited number of allergens tested Limited availability Rapid transportation required
Memory lymphocyte immunostimulation assay (MELISA)	Stimulation Index of lymphocytes	Limited evidence
Leukocyte migration inhibition test (LIF)	Migration activity of mixed-population leukocytes	Lack of sensitivity for detecting type IV reaction over the long time Typical antigens used may be not adequate
Lymphocyte activation test (LAT)	Expression of CD69 antigens	Limited evidence

addition to that, frozen sections or samples stored in special buffer solutions may be used for analysis of cytokine profiles.

In vitro tests require advanced laboratory prerequisites and are financial demanding compared to *in vivo* test options. Among them, the lymphocyte transformation test (LTT) is performed most commonly, in particular when patch tests reveal inconclusive results. The LTT is an objective test, quantifying the proliferation of lymphocytes after activation through potential allergens. Memory lymphocyte immunostimulation assay (MELISA) is a modification of the LTT and also known to investigate hypersensitivity. The leukocyte migration inhibition test (LIF) measures the migration activity of mixed-population leukocytes, using the fact that leukocyte migrate less fast when confronted with sensitizing allergens. The lymphocyte activation test (LAT) evaluates the expression of CD69 on peripheral blood mononuclear cells after stimulation with metal ions. None of those *in vitro* tests have been established for routine use.

Components released from implants may function as haptens. Nickel, cobalt, chromium and beryllium are metals known as sensitizers. Occasional hypersensitivity responses have been associated with tantalum, titanium, vanadium [4]. Among dermatitis patients, metal co-reactivity is a common phenomenon and may occur as cross-sensitization, most commonly seen between nickel and cobalt, and concomitant sensitization [11]. A critical interpretation of positive patch tests as well as the determination of clinical relevance is therefore essential.

Hypersensitivity reactions due to non-metal haptens have also been reported. Already in 1979, a case study reporting recurrent sterile fistula and aseptic prosthesis loosening as a result of hypersensitivity to the bone-cement component benzoyl peroxide has been published [12]. Apart from orthopaedic and trauma surgery, other fields of medicine are affected from hypersensitivity to polymethyl methacrylate (PMMA) as well, in particular aesthetic surgery or dental medicine. Significantly higher proliferative cellular responses to PMMA particles in patients with total joint arthroplasties at revision surgery due to aseptic loosening have

been reported compared to patients at either primary surgery or revision surgery due to mechanical reasons. At follow-up, reduction in *in vitro* cytokine production to PMMA was observed, corresponding to pain relief and functional improvement following revision surgery for aseptic loosening [13].

We investigated the immunomodulation of periprosthetic tissue as a result of release of PMMA debris in a study of 36 patients undergoing two-stage revision surgery for infected total joint replacement. Standardized tissue sampling was performed according to a strict protocol during explantation and reimplantation. Histomorphometric analysis, immunohistochemistry and the modified Willert Score were used to characterize the immunologic response. Infrared microscopy/spectroscopy confirmed the presence PMMA particles. We found significantly different score for perivascular and diffuse arrangement of CD3, CD20, CD11c and IL-17 positive cells and concluded that articulating PMMA spacers may immunomodulate the synovium and periprosthetic tissue (Singh et al., article in press Bone and Joint Journal, 2016).

On a practical note, it may be emphasized that one of the most common allergens in bone-cement, benzoyl peroxide, is challenging to test since it may elicit irritant patch test reactions. In doubt, another test kit may be used [14].

It may be reasonable to assume that due to the increasing numbers of implants, the topic of bone-cement related hypersensitivity will gain in importance in the future. Associations between allergies to antibiotics, exposure through (antibiotic-loaded) bone-cement and clinical symptoms are currently under investigation. However, there is still very little known about hypersensitivity towards bone-cement as present literature focuses on metal-related hypersensitivity.

In conclusion, the ideal diagnostic work-up of implant-related hypersensitivity in orthopaedic and trauma surgery remains controversial. It is highly recommended that tests for implant-related hypersensitivity are performed and interpreted by experienced teams. A final diagnosis should be in line with relevant clinical findings.

4. Are predictive tests useful?

As in any other field of medicine, the surgical community is looking for tests in order to prevent an adverse event from happening. However, given the evidence so far, predictive tests are not useful. A meta-analysis by Granchi et al. comprising 22 articles published between 1970 and 2011 investigated the benefit of metal hypersensitivity testing in patients prior to total joint replacement surgery. Their findings did not show any predictive value for positive or negative screening test results [3].

A recent study by Münch et al. used data from the Danish Knee Arthroplasty Register including primary and revision surgeries and compared them with data from a contact allergy patch test database. Their findings showed that the prevalence of contact allergy to nickel, chromium and cobalt was similar in patients of both subgroups (primary and revision). However, with increasing number of revision surgeries, the prevalence of cobalt and chromium hypersensitivity was clearly increasing as well. Interestingly, the results showed that the diagnosis of metal allergy before implantation did not lead to a higher risk of implant failure or revision surgery [15].

Despite the absence of convincing evidence and additional costs, most papers mention that predictive tests may have a role to play, in particular in patients with suspected implant-related hypersensitivity or a history of aseptic loosening. In those cases, most surgeons prefer doing a patch test. However, it should be noted that the more haptens are tested, the more likely a positive patch test will result [16] and the authors would like to emphasize again the importance of an extended series of potential haptens when using patch tests for hypersensitivity detection. Using biomarker as a predictive test may change diagnostic work-up in the future. Further studies are needed to be done in this context.

There is a large number of retrieval analyses and blood tests. Evidence is not supporting any causal relation between serum ion levels and metal hypersensitivity. However, an association between periprosthetic tissue metal content and hypersensitivity appears likely. We have investigated 28 total hip implant retrievals undergoing revision surgery. Histomorphologic, immunohistochemistry and periprosthetic tissue metal content determination were performed and correlated with intraoperative findings. Tissues displaying a predominantly lymphocytic response had a significantly higher metal content compare to samples with a macrophage-dominated tissue response ($222.2 \pm 52.9 \mu\text{g/g}$ vs $3.0 \pm 0.9 \mu\text{g/g}$, $P=0.001$). In contrast to that, there was no significant difference in the mean metal serum content between the two subgroups ($60.7 \pm 13.4 \mu\text{g/L}$ vs $43.7 \pm 3.8 \mu\text{g/L}$, $P=0.105$). We have concluded that periprosthetic tissue metal content but not serum metal content predicts the type of tissue response in failed small-diameter metal-on-metal total hip arthroplasties [17].

In conclusion, using predictive tests as a standardized screening tool for all patients undergoing total joint arthroplasty (TJA) or any other form of surgical implant is not recommended in order to avoid unnecessary expenses as well as positive test results in asymptomatic patients. However, patients with a history of implant-related hypersensitivity or aseptic implant failure may benefit from tests prior to surgery. Further work needs to be done in order to assess in which patients predictive hypersensitivity testing may be of benefit.

5. How to treat hypersensitivity to implants?

There are currently no general accept treatment algorithms for implant-related hypersensitivity. Moreover, there is a lack of evidence in large-scale studies regarding the ideal treatment option. Management currently mostly relies on individual case-by-case

decisions and reported outcomes of revision surgeries are rare (Table 2).

A multimodal approach depending on the scenario has been recommended in a joint position paper in 2008 by the Implant Allergy Working Group (AK 20) of the German Association of Orthopaedics and Orthopaedic Surgery (DGOOC), the German Dermatitis Research Group (DKG) and the German Society for Allergy and Clinical Immunology (DGAKI) [28]. According to that statement, the following issues should be considered: in patients with a new fracture, time is pressure. Given the fact that the implants are lying closely under the skin, the material of choice for osteosynthesis is titanium.

Patients undergoing orthopaedic surgery should be assessed thoroughly. The use of predictive tests has been discussed above. From an allergy point of view, known sensitizing materials should be avoided. However, orthopaedic considerations for the most appropriate implant choice need to be taken into account and mechanical aspects are equally essential. At any case, a detailed discussion with the patient and his/her relatives is highly recommended. Areas of concern should be addressed from both sides and be documented properly. An educated patient, being aware of advantages and disadvantages of each option, leading to a shared decision should be the ultimate aim. In general, metal-on-metal couples are considered being of a higher risk to hypersensitivity compared to metal-on-polyethylene implants. And more patients with hypersensitivity reactions to cobalt-alloy implants and stainless steel compared to titanium-based implants have been reported. Different options for metal sensitized patients exist and include using non-metal components such as ceramic-polyethylene couples, non-sensitized metal components namely titanium and newer implant modifications which will be discussed in more detail in the following paragraph. With regards to hypersensitivity to bone-cement, non-cemented replacements may be considered if possible. Alternatively, the component related to hypersensitivity may be avoided and/or replaced.

In patients with implants developing postoperative complications, a thorough diagnostic work-up needs to be done. Differential diagnoses (discussed in more detail in the last paragraph), need to be excluded, most importantly periprosthetic joint infection (PJI). Thereafter, postoperative tests for hypersensitivity may be considered, including taking history, clinical assessment, patch test and radiologic imaging. Tissue sampling may further help to guide management. Once the results are leading towards implant-related hypersensitivity or adverse tissue reaction, there is an indication for revision surgery whose extent depends on intraoperative findings, allergic component, age, level of activity and overall condition of the patient. Again, the authors would like to emphasize on the necessity of a detailed discussion with the patient and a proper documentation.

The authors follow the suggestions provided by the European Federation of National Associations of Orthopaedics and Traumatology (EFORT) on metal-on-metal THAs. According to these suggestions, systematic follow-up is recommended for all patients with MoM implants. There are specific recommendations for MoM THAs which include a follow-up for small-diameter heads in asymptomatic patients with a similar frequency compared to conventional THA. For patients with large-diameter head MoM THA, an annual follow-up is recommended and also for patients who underwent hip resurfacing during the first 5 years after index surgery. In patients with specific risk factors, an annual follow-up is recommended for the life of the joint. Imaging should include x-rays for all patients and in case of any abnormality or cobalt-levels above a certain threshold (within the range of 2 to 7 $\mu\text{g/L}$) additional imaging techniques such as ultrasound, CT-scan and/or [metal artefact reduction sequence] MARS-MRI are recommended as well as additional follow-up. Indications for revision include the

Table 2
Summary of case reports on management of implant-associated hypersensitivity reactions.

Reference	# of patients	Symptoms	Hypersensitivity testing	Treatment (revision implant component)	Results
<i>Suspected metal hypersensitivity</i>					
Dietrich et al. (2009) [18]	4	Swelling, persistent pain, recurrent effusion, soft tissue oedema	1 History: cutaneous metal intolerance Patch test: Ni LTT: Ni 2 History: cutaneous metal intolerance Patch test: Ni LTT: Ni 3 History: cutaneous metal intolerance Patch test: Co LTT: Ni, Co 4 History: cutaneous metal intolerance Patch test: Ni, Co LTT: Ni	1–3 Revision (titanium) 4 Revision (cementless TKA, titanium)	No swelling/effusion/oedema, and sig decrease in pain
Bergschmidt et al. (2012) [19]	1	Persistent pain, effusion, hyperthermia, ROM: 10–30°	Allergometry: Ni, PdCl2	Revision (cemented, ceramic)	ROM 0–90°, no swelling/effusion, sig decrease in pain
Van Opstal and Verheyden (2011) [20]	1	Pain, skin rash, diffuse swelling	History of hypersensitivity to osteosynthesis material Patch test/LTT	Revision (oxidized zirconium [oxinium])	Resolve of skin rash, minimal pain, good ROM
Thomas et al. (2015) [9]	9	Not reported	Patch test/LTT	Revision (8 × Ti-based surface coating, 1 × oxinium based implant)	Improved WOMAC score for 8/9 patients
Thomsen et al. [21]	1	Persistent pain, eczematous reaction	LTT negative	Revision (anti-allergic ZrN multilayer-coating on a standard CoCr29Mo6 implant)	Resolution of eczema, ROM 0–115°, no pain
Gupta et al. (2015) [22]	1	Pain, ROM: 10–110°, mild-moderate effusion, instability, progressing osteolysis	Possible history of metal sensitivity for bilateral MoM THAs Elevated serum Co, Cr Leukocyte sensitivity test: ↑reactivity to Al, Va, Mo, Ni Patch test: Cr Highly ↑serum Cr	Revision (oxinium femoral component, titanium-based tibial baseplate)	No pain, ROM: 0–120°, no joint effusion
Gao et al. (2011) [23]	1	Eczema, ROM: 3–126°, HSS score: 86	Patch test: Co, Cr, Mn	Revision (oxinium, Zr-2.5Nb)	Resolution of eczema
Oiso et al. (2004) [24]	1	Erythema, arthralgia, oedema, fever	Patch test: Co, Cr, Mn	Revision (ceramic, titanium)	Resolution of erythema and pain
<i>Suspected bone-cement hypersensitivity</i>					
Gamez (2015) [25]	1	Persistent pain, stiffness, soreness, ROM: 3–95°	Patch test: ethyl and methyl methacrylate, hydroxyethyl methacrylate	Revision (porous ingrowth component)	ROM: 0–125°, resolve of pain
Kenan et al. (2016) [26]	1	Pain, ROM: 0–100°, mildly fluctuant, tender soft tissue mass, severe joint effusion	History of allergic reaction to methyl methacrylate Histology: ALVAL reaction	Complete removal of the pseudotumor, extensive synovectomy, patient declined implant revision	No pain, ROM: 0–100°, mild joint effusion, no palpable mass
Bircher et al. (2012) [14]	5	Chronic pain, swelling, eczema, loosening, cutaneous infiltrate, generalized pruritus	1 Patch test: benzoyl peroxide, Co 2 Patch test: Benzoyl peroxide, methylchloro-isothiazolinone/methylisothiazolinone, Palacos®, p-tert-phenol formaldehyde resin, Co 3 Benzoyl peroxide, sodium metabisulfite, methyldibromo glutaronitrile 4 Benzoyl peroxide, rhodium chloride, sodium lauryl sulfate 5 Benzoyl peroxide	1 Arthrodesis 2 Revision (uncemented TKA) 3 one side: Arthrodesis, other side: Revision (uncemented TKA) 4 Removal of cement 5 Not done	Resolve of symptoms
Edwards et al. [27]	1	Pain, swelling, skin rash, tenderness	Patch test: benzoyl peroxide → ulcer History of hypersensitivity to benzoyl peroxide	Revision (uncemented TKA)	Minimal pain, resolve of skin rash, no swelling

HSS: hospital for special surgery-score; THA: total hip arthroplasty; TKA: total knee arthroplasty; ROM: range of motion; Sig.: significant.

following statement: “In asymptomatic patients, small fluid collections indicative of (adverse reaction to metal debris) ARMD need close monitoring (repeated imaging is recommended). In symptomatic patients and/or patients with progressive osteolysis, large or expanding pseudotumor, and/or progressive neck thinning, and/or cobalt-ions above threshold level, revision should be considered”. The multidisciplinary statement further makes recommendations regarding the appropriate management for elevated metal ions in asymptomatic patients including the confirmation of elevated levels in asymptomatic patients through repeated measurement. “Above a threshold of 2 to 7 $\mu\text{g/L}$ and pathologic results in additional imaging or further significant increase of cobalt-levels, revision surgery should be considered. And in case of excessive elevation, revision surgery should be discussed with the patient [29].

In conclusion, there is little evidence regarding the ideal treatment option for hypersensitivity in orthopaedic and trauma surgery. Management currently mostly relies on individual case-by-case decisions and should include allergenic and orthopaedic/trauma aspects. A detailed and well-documented discussion with the patient is essential.

6. Which implant modifications do exist?

Alternative implants may be considered in patients with (suspected) metal-related hypersensitivity. “Hypoallergenic” implants are manufactured by several companies. These alternatives include materials based on ceramic, titanium or oxinium as well as surface modifications of conventional implants and have been discussed in more detail by Bader et al. [30].

Titanium is known for its excellent biocompatibility. Different options of surface modification have been described in order to increase its resistance to wear such as oxygen diffusion hardening (ODH), nitrogen-ion implanted mechanisms, diamond-like-carbon (DLC) coating and physical-vapour-deposition-(PVD-) coatings. Surface modifications are not only available for titanium but also for cobalt-chromium alloys and are performed by various companies worldwide.

Oxidised zirconium is a patented material (oxinium) characterized as a metallic alloy with a ceramic surface. Its particular feature is formed by thermally driven oxidation and known as a surface transformation and not as a coating. It contains only a trace of nickel (0.0035%) and is therefore considered hypoallergenic. A retrospective analysis of more than 60,000 primary cases showed no greater risk of all-cause, aseptic and septic revision of oxidized zirconium femoral implants compared to traditional cobalt-chrome-polyethylen (CoCr-PE) bearings at a mean follow-up period of 2.9 years (interquartile range [IQR]: 1.5 to 4.4) [31]. So far, there is insufficient data with regards to long-term performance.

Using “biologically inert” materials such as ceramics is another option and well-established. Current gold standard for ceramic materials is the BioloX delta, an alumina matrix composite, which belongs to group of mixed oxide ceramics (alumina, zirconia, chromium oxide and strontium oxide), combining properties of alumina and those of yttrium-stabilized zirconia [32].

Drawbacks of these alternatives to conventional implants may include higher costs and increased surgical time in the beginning due to the need of becoming familiar with a new implant. Other areas of concern include cracking, gouging and delamination of coatings/modified surfaces, potentially resulting in third body wear and implant failure [33].

Results of a representative survey in Germany among members of the working group for joint replacement (AE) revealed that 84% of surgeons would prefer using hypoallergenic coated implants in total knee replacement surgery. Approximately every fifth

surgeon would prefer multilayer-coating or other modifications of their standard implant and almost one third is hoping for benzoyl peroxide-free cement. Despite the fact that most knee replacements are currently performed in a cemented way, 72% of the interviewed surgeons reported that they would decide to do an uncemented knee replacement in patients with a known hypersensitivity to bone-cement [34].

In conclusion, a number of implant modifications has been proposed and is currently subject of debate. Alternative options include materials based on ceramic, titanium or oxinium, as well as implants with (multilayer) surface coatings. Further works needs to be done in order to evaluate which patients may benefit from hypoallergenic implants and large-scaled studies are needed to investigate long-term implant survival.

7. What are the differential diagnoses to hypersensitivity?

As discussed, hypersensitivity reactions to implants in orthopaedic and trauma surgery are a diagnostic challenge. As the diagnosis of implant-related hypersensitivity may have major implications with regards to further treatment, differential diagnoses need to be ruled out. Most importantly, infectious aetiology needs to be excluded.

Several definitions for periprosthetic joint infections (PJIs) have been reported. The authors favor the one proposed by the recent Philadelphia consensus guidelines for PJIs, defining a PJI as “two positive periprosthetic cultures with phenotypically identical organisms, or a sinus tract communicating with the joint, or having three of the following minor criteria: (i) elevated serum C-reactive protein and erythrocyte sedimentation rate, (ii) elevated synovial fluid white blood cell count or ++ change on leukocyte esterase test strip, (iii) elevated synovial fluid polymorphonuclear neutrophil percentage, (iv) a single positive culture”. However, it is mentioned that “PJI may be present without meeting these criteria, specifically in the case of less virulent organisms” [35]. The diagnostic dilemma is represented in particular by low-grade infections with non-specific symptoms, false-negative cultures and inconclusive blood test. Low virulence of pathogens and their ability to form biofilm aggravate the diagnostic problem. A clear differentiation between infection and hypersensitivity may be even impossible.

Currently, histopathological evaluation of periprosthetic tissue is one of the most accurate methods in detecting low-grade infection. This was confirmed by a meta-analysis by Tsaras et al. including 3269 patients. They investigated the utility of intraoperative frozen section histopathology in the diagnosis of PJI [36]. However, the authors did not manage to show the optimal number of polymorphonuclear leukocytes (PMNs) per high-power field to establish a statistically significant diagnostic threshold between aseptic and septic loosening in their analysis.

Microbiological culture results need to be evaluated critically. As in any surgical procedure, contamination of the obtained tissue sample needs to be ruled out. Moreover, a sufficient incubation time is essential since it has been shown that prolonged culture for 14 days is improving the detection of slowly growing bacteria such as *Propionibacterium* species, instead of only revealing early-detecting species like staphylococci [37].

Data from implant-related infections in the context of orthopaedic and trauma surgery are inconsistent. In general, the risk is indicated as below 1–2% [38]. In conventional revision arthroplasty, infection rates are considered being between 3–5% whereas in the context of megaprotheses, re-infection rates as high as 43% after two-stage exchange arthroplasties have been reported [39,40].

Other differential diagnoses of hypersensitivity reactions may include mechanical failure and aseptic loosening due to

malalignment and instability. In most cases, a meticulous work-up including clinical assessment and radiologic imaging may guide direction.

In conclusion, most common differential diagnoses comprise mechanical failure and infection. The latter may be particularly difficult to rule out. However, diagnostic work-up is crucial since it guides further treatment.

8. Summary

Hypersensitivity reactions to implants in orthopaedic and trauma surgery are considered as a delayed-type of hypersensitivity reaction (type IV), characterized by an antigen activation of sensitized T-lymphocytes releasing various cytokines and may result in osteoclast activation and bone resorption. Potential happens are originated from metal alloys or bone-cement. Symptoms associated with implant-related hypersensitivity have been shown in various reports. However, there is little known about the exact prevalence and underlying pathomechanisms. With aging population, increasing numbers of total joint replacements implanted and consequently growing absolute numbers of complications, implant-related hypersensitivity are expected to increase in the future. Currently, generally accepted diagnostic algorithms are missing. There is no convincing evidence for predictive hypersensitivity testing. Since there is a lack of evidence on large-scale studies with regards to the ideal treatment option, management mostly relies on individual case-by-case decisions as for now. In patients with established diagnosis of hypersensitivity reaction, revision surgery is indicated. Different options for implant modification exist, but studies investigating long-term performance of hypoallergenic implants are required. Although challenging, differential diagnoses such as mechanical failure and periprosthetic joint infections need to be excluded. Further studies are needed to be done in this context. We expect the detection of predictive biomarkers in the nearer future as a major contribution.

All in all, management of patients with (suspected) implant-related hypersensitivity remains a challenge in orthopaedic and trauma surgery.

Disclosure of interest

The authors declare that they have no competing interest.

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