Metal Implant Allergy as a Differential Diagnosis of Periprosthetic Joint Infection

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Introduction

As a consequence of the increasing use of metal implants, we can expect to see more complications. In 2011 in Germany alone 168,486 total knee and 232,320 total hip arthroplasties were performed. Of these, 9.5% and 10.4% respectively were revisions due to complications.1 In the US the corresponding figures were 702,415 and 465,034 respectively, with revision rates of 8.4% and 10.7%. One of the triggers for complications is periprosthetic joint infection, which has a percentage frequency in the low single-digit range. The figures in the literature range from about 0.5% to 5%, with comorbidities and revision procedures increasing the risk.2,3 The diagnosis of periprosthetic joint infection becomes a challenge particularly if the bacterial count is low or no microorganisms can be detected, such as is the case with low-grade infections. Another issue that has been attracting more attention in recent years is that of hypersensitivity to implant metals and bone cement components. In the following we would like to discuss these issues from an allergology and immunology perspective.

Does hypersensitivity to metal implants exist?

Cutaneous metal allergy, such as that due to occupational exposure or the wearing of fashion jewelry components, is common. As a result, the rate of contact allergy in the total population is about 13% for nickel (Ni), 3% for cobalt (Co) and 1% for chrome (Cr).4,5 Women are usually affected more often – particularly against nickel. Implant allergy on the other hand appears to be rare compared to cutaneous metal allergy. However, as early as the 1970s there was a link made between implant failure and metal allergy.6 These cases were usually isolated or consisted only of small case series as was reported in more recent review papers6–8, although there are still no clear summary data available. Nevertheless, the Australian joint registry has included metal sensitivity as a cause of implant revision for the first time, and this was recorded as the reason for 0.9% of revisions in shoulder and 5.7% in hip arthroplasty.10 It must be noted, however, that it cannot be assumed from these figures how often this corresponds to an allergy / hypersensitivity. All the same, we showed in a study funded by the Bavarian State Ministry of Health of 300 implant patients that, compared to implant patients who were free of symptoms, those patients affected by complications had higher allergy rates against alloy metals or bone cement components.11

Clinical symptoms

Of course, local or generalized skin symptoms direct attention to a suspected allergy. These symptoms include eczema, livid erythema resembling erysipelas, impaired wound healing and isolated cases of vasculitis or urticaria. In these cases a metal allergy is usually identified. Eczema reactions to osteosynthesis material have also been observed (Fig. 1). Skin symptoms resulting from bone cement allergy are possible but providing evidence is difficult.
Accordingly, the aim should be histological investigation of implant-associated skin symptoms, as described for the example of a pseudoerysipelas-like reaction, to avoid overlooking a periprosthetic infection and other rarer constellations such as reticular erythema or intralymphatic histiocytosis.12

Other manifestations of an implant allergy have been described, including impaired wound healing and — particularly for knee implants in our patient collective — pain, recurrent effusions, restricted mobility and loosening without infection.13 Metal allergy may also play a role in the following constellations, but this is difficult to verify: aseptic implant loosening with peri-implant osteolysis; pseudotumor formation with metal-on-metal hip endoprostheses; excessive periarticular fibrosis (arthrofibrosis).

Clarification of cases of suspected allergy

Common causes, specifically periprosthetic joint infection (see below), must be excluded using differential diagnosis. The following steps are carried out during investigation of cases of suspected metal implant allergy:14,15

**Epicutaneous testing**
This enables standardized detection of metal allergy (specifically against Ni, Co and Cr) and contact allergy against bone cement components. However, a cutaneous allergic reaction cannot be equated 100% with the peri-implant constellation.

**Histology**
This can identify infection, particle-induced foreign-body reaction, fibrosis and inflammatory lymphocyte surface expression patterns. However, there is no definition of peri-implant histological hypersensitivity symptoms yet, and the causal trigger therefore cannot be identified.

**Lymphocyte transformation test (LTT)**
A T-cell metal sensitization can be revealed with this in-vitro procedure although it has been the preserve of scientific laboratories to date and requires the clinical relevance to be carefully checked. A recent review shows the diagnostic steps and a corresponding algorithm.16

Periprosthetic joint infection

An international consensus conference held in Philadelphia (USA) in 2013 defined joint infection and the steps required for its diagnosis.2 According to the definition, an implant-associated infection is present if

- there is a sinus tract (fistula) communicating with the joint or
- three of the following minor criteria are met:
  - elevated C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR)
  - elevated synovial white blood cell count or change in the leukocyte esterase test strip reaction
  - elevated synovial neutrophil percentage
  - positive histology for the peri-implant tissue
  - a single positive culture

The threshold for the criteria listed above, the culture period, histology criteria and additional instrument-based techniques (such as radiography and sonication) were also defined at this consensus conference.

Figure 2 shows a patient with a suspected periprosthetic joint infection. The histopathology of the tissue samples taken can also provide sensitive information about low-grade infections using the neutrophil threshold (more than 23 in 10 high-power fields [HPF] or normal maximum 5–10 neutrophils per HPF in 5 or more HPF). The values indicated in the paper published by Morawietz et al. in 2009 are therefore within the currently defined limits. Repeat biopsies (as also required for microbiology) are recommended.

Other diagnostic methods may also become available in the near future, such as supplementary analysis of antimicrobial peptides in the synovial fluid or the peri-implant tissue.17

In routine clinical practice, however, suspected cases of periprosthetic joint infection often cannot be verified for many patients. False-positive results due to contamination and false-negative results due to too few biopsies or slow-growing microorganisms (which are missed if the incubation period is too short) lead to uncertainty.

The clinical examination also often reveals only minor inflammatory symptoms with moderate warmth, effusion and pain. Consequently, a diagnostic procedure in line with the consensus conference is recommended, whereby the sampling should be repeated in case of doubt.
Procedure from an allergological perspective

If mechanical causes, misalignment, periprosthetic joint infection and other common differential diagnoses are excluded for arthroplasties affected by complications, then an allergic reaction should be considered as having triggered the symptoms. For this purpose, the summary of the epicutaneous testing and histology is required. The LTT can provide additional information about metal sensitization if it is carried out correctly, but it is not yet a widely used, routine procedure. Several working groups are currently determining other characteristics of patients with implant allergy. What is certain is that metal implant allergy exists but is often overlooked. Follow-up studies will indicate under which conditions patients will benefit from hypoallergenic implants.

Fig. 2: Patient with clinically suspected infection (differential diagnosis of implant incompatibility)

Literature

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Burkhard Summer has developed and evaluated in-vitro tests for the detection of metal hypersensitivity and sensitivity to newly developed biomaterials.

Correspondingly, he has performed many research projects in the field of implant allergy and studies concerning the biocompatibility of implant materials. The scientific goal of his work is the characterization of findings typical for patients’ excessive immune reaction to implants. The main methods used are the assessment of mediator production and molecular cytokine expression of patients’ blood cells or tissue samples.

Together with Peter Thomas, MD, PhD, Burkhard Summer runs a special outpatient ambulatory for patients with suspected implant intolerance reactions. More than 1,500 patients have already been seen in this special ambulatory.

Burkhard Summer has published the results of research projects and clinical studies in international journals. In addition, he takes active part in the education and supervision of postgraduate students in the fields of immunology and allergology. He is very interested in research contacts and academic discussion with international research groups.

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In 2007, “The Economist” opined in a cover article that many of the big human and social problems are biological. The question how to deal with periprosthetic joint infections (PJI) is one example. The article postulated that biology will be to the 21st century what physics was to the 20th century.

A paradigm shift is looming in arthroplasty. While tribology was the central and overriding issue in the 20th century in arthroplasty, in the 21st century it will be biology. The science and multidisciplinary-based research will direct attention more closely on the biological relevance of wear and corrosion products with implants, on systemic risks which have not been adequately researched and on the characterization of interactions between body cells and implant surfaces.

Periprosthetic joint infections (PJI) are biofilm infections and are one of the most complex and unsolved biological problems, also in the context of implants. PJs are expected to impose a substantial burden on medical and socioeconomic systems in future. In a recent publication, scientists stated that PJI remains the leading cause of revision after TKA, affecting 0.4 to 4.0% of primary arthroplasties and that it is the third most common complication after THA, affecting 0.3% to 2.2%. They refer to a study performed in the USA, which estimates that the number of primary TKA and THA will increase by 673% and 174%, respectively, from 2005 to 2030. The annual cost of infected revisions incurred to US hospitals increased from $320 million to $566 million during the time period from 2001–2009 and has been projected to exceed $1.62 billion by 2020.2 With an increasing number of arthroplasties, a corresponding increase in the number of PJs is expected. The authors of this study predict that the burden of PJI over this period will increase from 1.4% to 6.5% after THA, and from 1.4% to 6.8% after TKA.

Because of this development, PJI and potential risk factors, corrosion and fretting with modular implants as well as adverse reactions to metal debris (ARMD) have become key issues at international conferences and in the specialist literature. CeraNews summarizes latest results.
RISK FACTORS, DIAGNOSIS AND NEW FINDINGS OF THE PJI

Preoperative malnutrition is often cited as an independent risk factor for PJI after aseptic revision surgery. This has recently been reconfirmed by 2 studies which demonstrated that malnutrition is a risk factor for acute PJI. A large proportion of patients who undergo arthroplasty are obese. An increased risk of PJI and poorer outcomes are discussed as the tip of the iceberg. Early diagnosis of PJI and accurate identification of the responsible germs is currently being discussed as an essential element of the management strategy. Studies found conventional culture methods based on periprosthetic tissue and synovial fluid to be of poor diagnostic sensitivity.

STUDY

Malnutrition increases the risk of PJI after revision THA and TKA

Cross et al. and Yi et al. (USA) reported that a consecutive series of 375 aseptic revisions (202 TKA, 173 THA) and 126 septic revisions was screened for malnutrition. They found malnutrition in 53.2% of the patients undergoing revision for PJI compared to 32.8% in the patient group undergoing revision for other reasons. 3.2% of the 375 patients with aseptic revision developed acute PJI. The incidence of PJI was 7.3% in the malnourished group compared to 1.2% in the adequately nourished group. Malnutrition was both an independent risk factor for septic revision and acute PJI after aseptic revision.

The authors pointed out that preoperative malnutrition was common in both obese and normal weight patients. They concluded that given the high risk of acute PJI in malnourished patients, surgeons should consider screening patients for malnutrition preoperatively and revision procedures should be performed only after all nutritional parameters have improved.

Future studies should assess the impact of a standardized screening protocol with subsequent correction of abnormal laboratory parameters suggestive of malnutrition on the risk of PJI to determine the potential causal relationship.

STUDY

Malnutrition increases the risk of transfusion and PJI

Chen et al. (USA) evaluated 214 primary TJA (118 knees, 96 hips) in a retrospective study. They found that malnourished patients received more transfusions, and that those who were transfused had a higher risk of PJI.

STUDY

Being overweight increases the risk of PJI after TKA

Swiss scientists have investigated whether obesity correlates with PJI after primary TKA. Zingg et al. (Switzerland) evaluated 2,816 primary TKA performed in 2,346 patients. The mean follow-up was 86 months. In their prospective study, the authors reported that an increased BMI was found more often in female patients and was associated with increased age and a higher rate of comorbidities. In their study, the authors detected a clear BMI cut-off of 35. A BMI ≥ 35 was associated with double the risk for revision (any reasons) and PJI. They observed that this effect was stronger in men than in women.

STUDY

Increased rate of PJI after MIS anterior approach (Smith-Peterson MIS)

In a cohort of 601 consecutive MIS THA (551 patients), Clausss et al. (Switzerland) found a higher rate of PJI (2.0%) compared to published data in conventional THA. They found a high rate of poly-microbial infection (58%), and among them fecal pathogens were found in 42% of the cases. A relatively high BMI was found for the PJI group. The authors suggested that a more lateral incision leading away from the groin might be beneficial, especially in obese patients.
In 2011, Holinka et al. (Austria) tested the sonication method according to recommendations by Trampuz et al. for all retrieved prostheses in their clinical diagnostic routine and confirmed a significant benefit for detecting germs from component surfaces compared with tissue culture. Recently further published studies confirmed that the sonication method is reliable and sufficient for pathogen detection in the clinical diagnostic routine.

2 STUDIES

Sonication improves the microbiological diagnosis of PJI

Ravn et al. (Denmark) included consecutive revisions of 126 THA and 77 TKA in a prospective study. Based on clinical and serological findings, the authors expected a PJI in 48 revision cases. They compared the sonication fluid culture of the removed prostheses with the conventional periprosthetic tissue culture and synovial-fluid culture. The authors reported that conventional culture methods diagnosed 49 cases of PJI (24%), of which 7 and 5, respectively, were revised due to aseptic loosening and mechanical failure. In contrast, a positive sonication-fluid culture was found in 68 cases (33%), of which 12 and 15, respectively, were revised due to aseptic loosening and mechanical failure. Among the 48 revision cases indicated by PJI, germs were identified by conventional methods in 37 cases (77%) and by sonication in 41 cases (85%). Contaminations found in revision cases were mainly due to mechanical reasons. The sonication led to fewer cases with contamination compared to conventional methods (15 and 6 cases, respectively).

The authors summarized that sonication detected 19 more positive PJI cultures compared to conventional methods, led to fewer contaminations and gave valuable information on the causative germs in a higher proportion of the revisions due to PJI.

Lepetsos et al. (Greece) investigated 64 patients with THA or TKA that were revised because of loosening of the prostheses. They compared the sonication-fluid culture of the explanted prostheses with conventional periprosthetic tissue culture for the purpose of microbiological diagnosis of PJI. The authors found a significantly higher sensitivity of sonication-fluid culture (84.6%) compared to the sensitivity of conventional tissue culture (61.5%).

New methods such as sonication of explanted implant components are revolutionizing the diagnosis of PJI. Cases that were initially interpreted as aseptic loosening can actually be identified as low-grade infections.
2 STUDIES:

Significantly higher bacterial adherence to PE components (TKA) and to XPE components (THA) compared to metal components

Unfortunately, significant clinical studies investigating the bacterial adherence to different explanted septic prosthetic components of knee prostheses, hip prostheses and others are lacking.

To our knowledge, so far the first study which confirmed experimental results of the higher bacterial adherence to conventional PE components (UHMWPE) compared to other implant materials was conducted by an Austrian research group in 2012. Holinka et al. (Austria) published important clinical findings of a study which evaluated and quantified the bacterial adherence on 100 different components of explanted total knee prostheses (femoral and tibial component, PE insert, patella) from patients with PJI. They evaluated the bacterial load of these knee component surfaces by counting the colony-forming units (CFU) using the sonication culture method. The authors reported that PE-inserts and tibial components were most often affected by microorganisms, although the difference was not significant in this study. The highest load of CFU was detected on PE components (insert, patella) compared to CoCrMo components. Staph. epidermidis adhered to the highest number of the knee components. Staph. aureus was identified as the pathogen causing the highest CFU count in the sonicate cultures. The authors pointed out that a partial component exchange or an exchange of single PE components in septic revision surgery may not be sufficient.

Recently, this research group published first important clinical results about the differential bacterial load on components of total hip prostheses in patients with PJI. Lass et al. (Austria) evaluated and quantified the bacterial adherence to 80 different hip components of retrieved prostheses (stem, cup, femoral ball head, insert) from 24 consecutive patients with PJI. They sonicated 16 titanium-aluminium-niobium alloy (Ti6Al7Nb) stems, 16 pure titanium cups, 24 ceramic femoral ball heads (BIOLOX®delta) and 24 XPE inserts.

All 24 prostheses (24 patients) showed positive sonication cultures. Germs were detected in 68 of 80 retrieved hip components. Staph. epidermidis was identified as the pathogen causing the highest CFU count, especially from the XPE inserts and was isolated from the majority of components.

The highest bacterial load was detected on XPE inserts (10,180 CFU; mean 566, range 0–5,000), followed by ceramic femoral ball heads (5,746 CFU; mean 319, range 0–2560), metal cups (5,007 CFU; mean 278, range 0–3000) and stems (1,805 CFU, mean 82, range 0–1000). The highest CFU load per component was detected on XPE inserts (566), followed by the metal cups (417) and ceramic femoral ball heads (338), whereas the CFU load for the pure titanium stems was much lower (164).

The authors pointed out that the important finding of this study was the significantly higher bacterial adherence to XPE inserts compared with metal implant materials (stem, cup), which confirms the lower bacterial adherence to metal (titanium, titanium alloy).

They reported that unequal distribution of CFU between ceramic femoral ball heads and XPE inserts was not significant, but showed that different biomaterials have an influence on the bacterial load.

We are however of the opinion, that evidence-based scientific studies are required that demonstrate significant clinical results and valid data about the bacterial load on different bearing surfaces.

EFFECT OF SMOKING ON FAILURE RATES IN PATIENTS WITH MoM BEARINGS

Cigarette smoke contains traces of cobalt and nickel. It is known that smoking affects both the innate and adaptive immune response. An association between smoking and an increased risk of nickel sensitization is already known from previous studies. For the first time, a study has now identified smoking as a potentially strong risk factor for failure of MoM bearings. This association was not evident in the compared patient group with CoP bearings.
STUDY

Smoking increases failure rate of MoM bearings in contrast to CoP bearings

Lübbeke et al. (Switzerland, USA) investigated the effect of smoking on revision rates in patients with cementless MoM THA compared to patients with cementless CoP bearings of the same cup design and ball head diameter (28mm). The study comprised 1,964 patients (57% female) with a mean age of 71 years. 1,301 CoP bearings and 663 MoM bearings were evaluated. The mean follow-up was 6.9 (1.8–12.8) years. 56 THA were revised. In patients with MoM bearings the revision rate occurring among ever-smokers was 4 times greater than among non-smokers (95% CI 1.4–10.9). In patients with CoP bearings the incidence rate was significantly lower at 1.3 (95% CI 0.6–2.5). The 6 patients in the study showing ARMD were ever-smokers.

The authors hypothesized that the interaction between smoking and MoM bearings may be related to metal hypersensitivity. The authors concluded that smoking might be a trigger or an effect amplifier for ARMD from MoM bearings.

OUTCOME OF CERAMICS

Ankylosing spondylitis is a form of progressive arthritis caused by chronic inflammation of the spine and sacroiliac joints. It can also affect the hip joints. Data available concerning the outcome of THA with different bearings in patients with ankylosed hips are limited. However, initial clinical studies show significant benefits of CoC bearings in terms of long-term survival. The absence of osteolysis and therefore preserved bone stock might make potential revision surgery easier. The excellent biological behavior of ceramic particles is reflected in the lower risk of wear debris-induced osteolysis.

2 STUDIES

High long-term survival rate of CoC THA in patients with ankylosing spondylitis

Kim et al. (Korea) reported a 30–50% incidence of hip involvement in patients with ankylosing spondylitis. They noted that problems in connection with THA include, among other things, the young age and difficult surgical procedure in these patients. The authors compared the clinical and radiological results of 49 cementless THA in 35 patients (30 male, 5 female). The mean age at the time of surgery was 32 (20–54) years. The mean follow-up was 9.1 (2.2–18.3) years. MoP bearings were used in 23 cases and CoC bearings were used in 26 cases.

The HHS showed no significant differences between the two patient groups. The radiological investigation showed osteolysis in 13 hips of the MoP group, whereas no osteolysis could be detected in the CoC group. Cup loosening was seen in 10 hips of the MoP group, whereas there was no loosened cup in the CoC group. The mean survival rate after 9.1 years was 100% in the CoC group compared with only 81% in the MoP group. The authors concluded that CoC bearings might be a preferable option in such cases of uncemented THA.

To our knowledge, so far the longest series of cementless THA in patients with ankylosed hips with a mean follow-up of 11 (5–19) years was published by Rajaratnam et al. (Australia) in 2009. These authors found similar results with CoC bearings in ankylosed hips. They evaluated 16 cementless THA in 15 patients (9 male, 6 female) with a mean age of 52 (16–75) years at the time of surgery. In patients operated prior to 1993, a MoP bearing (22.25, 28 mm) was used. Patients operated between 1993 and 1997 received a CoP bearing (28 mm). Patients operated after 1997 had a CoC bearing (28, 32 mm) implanted. All patients showed improved mobility and function postoperatively. However, 9 hips (8 patients) received MoP or CoP bearings. 6 hips (5 patients) showed linear wear between 1 and 3 mm on the latest X-rays. Radiographic osteolysis was seen in 3 hips. A young female patient with MoP bearing (22.25 mm) was revised 5 years after surgery due to aseptic loosening of the cup. The authors postulated that aseptic loosening was due to a combination of high functional demands of the THA in this 16-year old patient at the time of surgery, combined with relatively soft acetabular bone due to juvenile rheumatoid arthritis.

None of the 7 patients (7 hips) who received a CoC bearing showed any radiographic evidence of linear wear or osteolysis at the latest follow-up. They concluded that cementless THA allows an effective treatment of ankylosed hips with good longterm results.
Higher mid-term survival rate for CoC bearings vs. MoP bearings

Radulescu et al. (Romania) reported on mid-term results of a prospective study comparing cementless CoC THA (alumina) in 60 patients (38 female, 22 male) with a mean age of 45.6 (30–62) years and cementless MoP THA in 62 patients (41 female, 21 male) with a mean age of 46.8 (32–64) years. The mean follow-up was 6.2 (4.1–8.9) years. The radiological investigation showed osteolysis in 4 hips of the MoP group (6.45%), whereas osteolysis could be detected only in a single case of the CoC group (1.67%). The HHS showed no significant differences between the two patient groups.

The authors concluded that CoC bearings have a higher survival rate at 6 years postoperatively than MoP bearings.

Retrieval analysis confirms excellent long-term wear behavior of the CoC bearing

Korim et al. (UK) studied 9 retrieved CoC bearings of the first generation of the so called “Mittelmeier prostheses”, which were revised for aseptic loosening after a mean of 16 (7–20) years. The ceramic components were alumina ceramic (BIOLOX®, CeramTec GmbH, Plochingen). The mean age of the patients (6 female, 3 male) was 48 (22–60) years at the time of primary surgery.

The authors reported that only 3 femoral ball heads showed areas of stripe wear with significantly higher surface roughness than minimally worn areas (0.645 µm vs. 0.289 µm). The remaining 6 bearings showed minimal wear (0.289 µm as opposed to smooth surface 0.011 µm).

They concluded that the first generation of CoC bearings still showed less wear over a long time period compared to previous retrieval analyses.

NEW FINDINGS ABOUT CORROSION: INFLAMMATORY CELL INDUCED CORROSION (ICIC) OF CoCrMo HIP AND KNEE IMPLANTS

Corrosion damage affecting the local biological system has been analyzed and discussed in a large number of publications. Recently published new evidence of corrosion damage caused by different inflammatory cell types is confronting scientists and clinicians with completely new questions concerning the clinical consequences of possible interactions between inflammatory cells and CoCrMo implant surfaces. These latest findings may also have an effect on our understanding of ARMD in joint replacements.

Inflammatory cells are able to corrode CoCrMo implants in vivo

Gilbert et al. (USA) presented new evidence of direct inflammatory cell-induced corrosion of CoCrMo implants from microscopic observations of retrieved hip and knee implants. Of the 69 CoCrMo retrievals from 51 implant systems, including MoM and MoP bearings, corrosion damage caused by inflammatory cells was detected in 51 components (74%).

The authors reported that these observations were not limited to any specific design, alloy microstructure, metal or polyethylene insert material.

They observed different specific patterns of corrosion, which implies that different cell types and/or cell activities were stimulated. Corrosion topographies seem to show that individual cells migrate across CoCrMo implants, attach and seal down their membrane on the surface to drive the corrosion. The authors observed that the attacking cells are between 20 and 300 µm in size. Metallic iron plays an important role in the inflammation of joints; it was found in the areas that had been subject to extensive corrosive attack by the cells. It is not yet clear, which conditions are necessary and which activation stimuli lead to this type of direct inflammatory cell attack and corrosion.

The authors speculated that activation stimuli may include tribocorrosion on bearing surfaces, modular tapers or other implant regions, particle generation from polyethylene implants, infection or unknown patient-specific factors.
It is still unknown whether such predisposing patient factors also play an essential role, similar to inflammatory diseases associated with a lower pH-value and changes in local environmental conditions.

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