Intolerance reactions to knee arthroplasty in patients with nickel/cobalt allergy and disappearance of symptoms after revision surgery with titanium-based endoprostheses

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Summary
Intolerance reactions to metal implants may present as dermatitis, impaired wound healing, effusions, pain or loosening. The clinical relevance of metal allergy in the differential diagnosis is often unclear and patients may even tolerate implants containing metals to which they are allergic. We present four patients with knee arthroplasty in whom after exclusion of infection or mechanical causes, a nickel/cobalt allergy led to replacement surgery with titanium-based prostheses. The subsequent alleviation of symptoms underlined the relevance and usefulness of allergological diagnostics in selected cases of complicated arthroplasty.

Introduction
About 125,000 knee joint endoprostheses are implanted yearly in Germany and are usually tolerated without complications. Besides classical causes of problems such as infections and mechanical factors, allergic reactions can also occur and manifest as dermatitis, impaired wound healing, or effusions as well as pain and limitation of motion [1, 2].
The role of allergy to implants is controversial. Despite the presence of a metal allergy, the implanted material is often tolerated [3]. In contrast to the rate of metal sensitization rates in the general population towards nickel (Ni) (on average 13.1 %) or cobalt (Co) (2.4 %) [4], hypersensitivity to implants remains rare, even though it as first mentioned in the 1960s [5]. Causative agents are likely to be Ni, Co and chromium (Cr). Isolated cases of allergic reactions to acrylate-based bone cements have been reported [6, 11]. Various authors have reported a higher rate of metal sensitization in complicated arthroplasty. A metal sensitization (13 to Co, 4 to Ni, 2 to Cr) was found in 16 of 35 patients with failure of metal to metal prostheses [7]. In a series of 44 patients with problems after knee arthroplasty, an increased rate of metal allergies of 20 % towards Ni, 14 % towards Co and 7 % towards Cr was observed [8]. We present the cases of four women with knee endoprostheses where no infection or mechanical factors caused the problems. The metal allergy found (Ni, Co) led to revision surgery with a titanium-based prostheses resulting in alleviation of symptoms.

Methods
Patient collective
We identified and followed the four patients in our implant allergy special clinic. Evaluation included a questionnaire-aided history, an expanded patch test series, and lymphocyte transformation test (LTT) as well as long-term observation. Four women with knee endoprostheses had pain and recurrent effusions. All four reported erythema, pruritus and dermatitis when wearing costume jewelry and wrist watch bands ("cutaneous metal intolerance").

Examinations
Patch test
Patch testing was performed with DKG (German Contact Allergy Group) standard series containing Ni, Cr and Co, an expanded metal series (manganese, molybdenum, vanadium and titanium preparations) as well as – if previously used in the patient – with the bone cement series. The latter contains 2-hydroxyethylmethacrylate, methylmethacrylate, copper sulfate pentahydrate ($CuSo_4 \cdot 5H_2O$), benzoyl peroxide,

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Figure 1: Swelling, slight erythema and overheating of the affected knee at presentation.

gentamicin sulfate, hydroquinone and N,N-dimethyl-p-toluidine. Reading was performed after 48 and 72 hours as well as after one week. The reactions were rated according to DKG criteria.

Lymphocyte transformation test

For the lymphocyte transformation test, blood was drawn before the patch test. The LTT with Ni, Cr, Co, Mo, Mn and Ti was performed as described by Summer et al. [9]. The proliferation response was stated as stimulation index (SI).

Results

Patient R.G. (64 years) had a total endoprosthesis of the right knee joint in April 2007 and developed recurrent swelling and effusions as well as continued pain and limitation of movement occurred. Six joint aspirates revealed no infectious agent. Fifteen years ago a nickel contact sensitization corresponding to cutaneous metal intolerance was found. At presentation, the right knee joint was swollen and warm. Renewed allergy diagnostics again demonstrated a nickel contact allergy. In the LTT, an elevated SI was found towards nickel. After switching to a titanium-plated endoprosthesis (June 2008) no further swelling or effusions occurred; pain appeared only after extensive use.

Patient E.S. (68 years) received a cement-free CoCrMo-based knee joint total endoprosthesis in March 2005. Since that time, she experience pain on movement and at rest as well as recurrent swelling and erythema. A sensitization to Ni and Co was known since 1995. The involved knee displayed erythema in the scar region and warmth. The current patch test confirmed a Ni contact allergy. In the LTT, an elevated SI towards Ni was observed. Since she was switched to a titanium-plated endoprosthesis (October 2006), she no longer has erythema or effusions but develops slight pain only after more extensive activity.

Patient B.M. (65 years) received a CoCrMo-based knee endoprosthesis with partial cementing on the patella in 1997. Due to recurrent effusions and pain, revisions were performed in 2004 and 2005. For years an intolerance to costume jewelry has existed. She presented with swelling, slight erythema and warmth of the involved knee (Figure 1). The current patch test revealed a Co contact allergy. The LTT showed elevated SI towards Ni and Co. A change of prosthesis to a titanium-plated endoprosthesis was performed in March 2007. Effusions and pain were relieved.

Patient M.K. (57 years) received a CoCrMo-based medial endoprosthesis in the right knee October 2003. In February 2004 a first revision was required because of early loosening. In September 2004, a second revision was done because of recurrent effusions and soft tissue edema. A femur portion of the prosthesis consisting of pure titanium and a CoCrMo-based cemented tibia portion were implanted. Due to persistent effusion and edema, allergy diagnostics were performed revealing sensitizations to Ni and Co as well as to ethylene glycol dimethacrylate, 2-hydroxy ethyl methacrylate and 2-hydroxy propyl methacrylate. The LTT revealed an elevated SI to Ni. On this basis in August 2007 the tibia portion was exchanged for a pure titanium component and residual cement was removed. She has been symptom-free since then.

The constellation of findings of the four patients is summarized in Table 1.

Discussion

Causes of the symptoms such as periprosthetic infection or mechanical factors were first excluded in our patients. Even though the respective implants are often tolerated despite Ni or Co allergies and it is not yet possible to identify "patients at risk", we consider freedom from symptoms after revision surgery using titanium-based endoprostheses as an indication of the clinical relevance of Ni/Co allergy. Intolerance of prosthesis materials can manifest as dermatitis, swelling, erythema, effusion as well as pain, limitation of motion and aseptic loosening [1]. Typical causative agents are Ni, Co and Cr. According to ISO 5832 refined steel contains about 13–15 % Ni, CoCrMo alloys as standard endoprosthesis material up to 1 % Ni and 65 % Co. Corrosion and abrasion lead to *in vivo* metal exposure [10]; from hardened bone cements only exposure to antibiotics such as gentamicin has been shown [11]. The standard allergy diagnostic tool in implant intolerance is the patch test, which includes Ni, Cr and Co in the standard series as well as acrylates, additives and gentamicin in a bone cement series. In contrast no reliably evaluated test substances exist for manganese, molybdenum, vanadium and titanium [12]. Prophetic testing is not sensible. In the analysis of periimplant tissue, only abrasion and infection-typical reaction patterns have been defined to date [13]. Periimplant lymphohistiocytic infiltrates can be an indication of intolerance reactions [14]. The LTT cannot be over-interpreted as an "allergy test", but at the most possibly indicates exposure and sensitization [15]. Epidemiologic data on metal implant allergy are lacking even in endoprosthesis registries. German patients with endoprostheses do not always possess an endoprosthesis passport and employed metal alloys and bone cements are difficult to identify. Finally, studies on the outcome of revision surgery with the intent to avoid allergens are lacking. Even if metal allergy does not signify endoprosthesis intolerance, Granchi et al.

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Table 1: Findings of the four patients.

	Endoprosthesis*)	Problems	Allergy history **)	Patch test	LTT	Course after revision ***)
Patient R.G., 64 years	Cement-free	Swelling, continual pain, recurrent effusions	CMI	Ni	Ni	No swelling / effusions, practically no pain****)
Patient E.S., 68 years	Cement-free	Continual pain, phases of swelling, erythema	AR, AA, CMI	Ni	Ni	No erythema / effusions, practically no pain****)
Patient B.M., 65 years	Partially cemented (patella)	Recurrent pain, effusions, swelling, erythema	AR, AA, CMI	Co	Ni, Co	No swelling / effusions, practically no pain****)
Patient M.K., 57 years	Partially cemented (tibia)	Recurrent effusions, soft tissue edema, early loosening	CMI	Ni, Co	Ni	No effusions or edema

*) CoCrMo-based knee endoprosthesis
**) AR: allergic rhinoconjunctivitis; AA: allergic asthma; CMI: cutaneous metal intolerance (costume jewelry, wrist watch band, jeans button)
***) Pure titanium prosthesis (patient M.K.), titanium-plated prosthesis (patients R.G., E.S. and B.M.)
****) Slight pain only after extensive use

described a shorter half-life of a hip joint endoprosthesis in allergic than in non-allergic patients [16]. Goals of the Munich Implant Registry (*http://allergomat.klinikum.uni-muenchen.de*) include more precisely defining patient characteristics and documenting the long-term course after revision surgery. Even if the clinical relevance of a diagnosed metal allergy in endoprosthesis intolerance is difficult to prove, affected patients can profit from allergy diagnostics. <<<

Conflicts of interest
None.

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References

1 Thomas P, Schuh A, Ring J, Thomsen M. Orthopädisch-chirurgische Implantate und Allergien. Orthopäde 2008; 37: 75–88; Hautarzt 2008; 59: 220–229.
2 Kubba R, Taylor JS, Marks KE. Cutaneous complications of orthopaedic implants. A two-year prospective study. Arch Dermatol 1981; 117: 554–560.
3 Carlsson A, Moller H. Implantation of orthopaedic devices in patients with metal allergy. Acta Derm Venereol 1989; 69: 62–66.
4 Schäfer T, Bohler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B, Wichmann HE, Ring. Epidemiology of contact allergy in adults. Allergy 2001; 56: 1192–1196.
5 Foussereau J, Laugier P. Allergic eczemas from metallic foreign bodies. Trans St Johns Hosp Dermatol Soc 1966; 52: 220–225.
6 Richter-Hintz D, Rieker J, Rauch L, Homey B. Prothesenunverträglichkeit bei Typ-IV-Sensibilisierung gegen Knochenzement. Hautarzt 2004; 55: 987–989.
7 Munro-Ashman D.; A.J. Miller. Rejection of metal to metal prosthesis and skin sensitivity to cobalt. Contact Dermatitis 1976; 2: 65–67.
8 Thomas P, Barnstorf S, Rueff F, Przybilla B, Summer B. Kontaktallergie gegen Endoprothesenkomponenten als mögliche Ursache einer Knieendoprothesen- Unverträglichkeit. Allergo J 2004; 13: 51.
9 Summer B, Sander A, Przybilla B, Thomas P. Molecular analysis of T-cell clonality with concomitant specific T-cell proliferation in vitro in nickel-allergic individuals. Allergy 2001; 56: 767–770.
10 Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. Clin Orthop 1996; 329 (Suppl): 233–243.
11 Thomas P, Schuh A, Eben R, Thomsen M. Allergien gegen Knochenzementkomponenten. Orthopäde 2008; 37: 117–120.
12 Geier J, Lessmann H, Becker D, Thomas P. Allergologische Diagnostik bei Verdacht auf Implantatunverträglichkeit: Hinweise für die Praxis. Hautarzt 2008; 59: 594–597.
13 Morawietz L, Gehrke T, Schröder JH, Krenn V. Histopathologische Diagnostik der Endoprothesenlockerung. Pathologe 2006; 27: 439–446.
14 Willert HG, Buchhorn, GH, Fayyazi A, Flury R, Windler M, Koster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 2005; 87: 28–36.
15 Brehler R, Merk H. In-vitro-Tests zum Nachweis von Kontaktallergien. Hautarzt 2005; 56: 1141–1143.
16 Granchi D, Cenni E, Trisolino G, Giunti A, Baldini N. Sensitivity to implant materials in patients undergoing total hip replacement. J Biomed Mater Res B Appl Biomater 2005; 77: 257–64.

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