

Original article

Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation

Background: In 16 patients with revised metal-on-metal arthroplasty and peri-implant lymphocytic inflammation, we verified the role of metal hypersensitivity by patch testing (PT) and lymphocyte transformation test (LTT).

Methods: In the 16 patients with lymphocyte dominated periprosthetic inflammation, allergy history was obtained by a questionnaire, specific serum IgE to aeroallergens was measured to assess atopy, PT to standard and metal series was performed and metal sensitivity was further assessed by LTT using blood mononuclear cells.

Results: Revision surgery was performed because of pain (8/16), osteolysis (4/16), dislocation (3/16) and loosening of the stem (1/16). Histological examination showed perivascular infiltrates of T lymphocytes, high endothelial venules, fibrin exudation and accumulation of macrophages with drop-like inclusions. Five patients had a history of cutaneous metal allergy and atopy was found in 25% of the patients. In 13/16 patients (81%), systemic metal sensitivity was found based on PT and/or LTT. Patch test reactions were seen in 11/16 patients (69%; partly multiple reactions/patient): 7/16 to Cobalt (Co), 7/16 to Chromium (Cr), 4/16 to Nickel (Ni), and one each to Molybdenum (Mo) and Manganese (Mn). Ten of 16 patients (62%) showed enhanced LTT reactivity to metals: 7/16 to Ni, 7/16 to Co, 5/16 to Cr, 5/16 to Mo and 4/16 to Mn.

Conclusions: The lymphocyte dominated peri-implant inflammation may well reflect an allergic hyper-reactivity in these patients, given the high rate of concomitantly found metal allergy. Despite the overall incidence of metal implant allergy being low, allergic reactions should be included as differential diagnosis in failed metal-on-metal arthroplasty.

**P. Thomas¹, L. R. Braathen²,
M. Dörig³, J. Auböck⁴, F. Nestle⁵,
T. Werfel⁶, H. G. Willert^{7*}**

¹Department of Dermatology and Allergology, Ludwig-Maximilians-University Munich, Germany; ²Department of Dermatology, Inselspital, University of Berne, Switzerland; ³Kantonsspital, Department of Orthopaedic Surgery, Münsterlingen, Switzerland; ⁴Kantonsspital, Department of Dermatology, University of Linz, Linz, Austria; ⁵Department of Genetics and Molecular Medicine, Kings College London School of Medicine, London, UK; ⁶Department of Dermatology, Hannover Medical School, Hannover, Germany; ⁷Department of Orthopaedic Surgery, Georg-August-University, Göttingen, Germany

Key words: allergy; arthroplasty; hypersensitivity; lymphocyte; metal; patch test; total hip replacement.

Prof. Dr P. Thomas
Department of Dermatology and Allergology
Ludwig-Maximilians-University München
Frauenlobstr. 9-11
80337 München
Germany

*Prof. Dr med. Hans-Georg Willert, initiator of this study, passed away on September 25th, 2006.

Accepted for publication 11 November 2008

Wear of the articular surfaces is still the most important limiting factor for a durable function of an artificial joint. The process of abrasive wear produces particles. When these particles come into contact with the surrounding tissue, they may cause a granulomatous foreign-body reaction, which can lead to bone resorption and loosening of the implants, resulting in the failure of the artificial joint function (1–4). Therefore, the reduction of abrasive wear is of significant importance.

This was the reason to re-introduce the metal/metal pairing for artificial hip joints. An examination of explanted cups and ball heads of 'classic' all-metal joints (e.g. of the McKee-Farrar type), made of CoCrMo-cast alloy, which have been implanted in the 1960s and 1970s, had shown remarkably low metal wear and release of metallic wear particles was also correspondingly low

(5–7). On the basis of this knowledge and of an improved manufacturing process, B. G. Weber began to implant metal/metal pairings of CoCrMo-alloy in St Gallen (CH) again in 1988, and thus marked the beginning of a renaissance of this material combination for the joint surfaces of artificial hips (8). Various manufacturers now offer this new generation of metal/metal joints for numerous hip endoprostheses.

The reported early and mid-term clinical results after 4–10 years are satisfactory (9–14) and measurements on retrieved implants confirmed a considerably reduced wear from the metallic joint surfaces (15). Failures of these artificial joints are rare and revision became necessary only in a maximum of one of 200 artificial hip replacements. In the case of failure, not wear related complications but rather a local hypersensitivity response of the

periprosthetic tissue, presumably to Cobalt (Co), Chromium (Cr), Molybdenum (Mo) or Nickel (Ni) ions was postulated. The morphological features of this lymphocyte dominated tissue response were claimed to resemble a delayed type hypersensitivity (DTH) reaction and were described by several authors for revised metal-on-metal joints (16–19).

Evidence for pathomechanisms and the central role of T lymphocytes in DTH reactions to metals comes from histopathological studies in contact dermatitis patients and studies dealing with metal (Ni)-induced lymphocyte reactivity *in vitro* (20–24). Based on the description of DTH-like reactions around metal-on-metal joints, we wondered whether such findings could be linked to systemically detectable metal hypersensitivity.

To answer this question, we performed patch testing (PT) for metal allergy and evaluation of *in vitro* lymphocyte reactivity to metals (lymphocyte transformation test, LTT) in a consecutive series of 16 patients from Switzerland, Germany and Austria who had surgical revision of a metal-on-metal hip joint with concomitant histopathological picture of periprosthetic lymphocyte dominated inflammation.

Materials and methods

Patients and controls

In the 16 patients (eight females and eight males; age range 52–83 years) revision surgery became necessary because of pain (8/16), osteolysis (4/16), dislocation (3/16) and loosening of the stem (1/16).

At revision, periprosthetic tissue was retrieved and fixed in formalin. At a later stage, heparinized blood (40 ml) was processed for assessment of lymphocyte reactivity to metals by LTT. In addition, serum samples were cryoconserved for IgE-measurement. Furthermore, PT was performed. Twelve nonallergic healthy individuals (five females and seven males; age range 25–76 years) volunteered as control blood donors for the LTT. Patients' data are given in Table 1.

Patient-based information about allergic diseases was obtained by the use of a questionnaire. This included family/personal history of atopic diseases (allergic rhinoconjunctivitis, allergic asthma and atopic eczema), of hypersensitivity reactions to drugs or insect sting and of cutaneous reactions to metals. The latter question included not only the skin changes upon use of jewellery, wristwatches and bracelets, but also cutaneous reactions in association with the implant. The study was approved by the ethics committee. All subjects gave informed consent.

Histological examination of periprosthetic tissue

Tissue specimens were taken mainly from the newly formed articular capsule, which in general has to be removed anyway in order to expose the implants. The formalin-fixed tissues were decalcified, if necessary, and 5–10 µm microtome sections were stained with haematoxylin–eosin, van Gieson and Giemsa methods. The sections were microscopically examined under normal light and with polarization (Olympus BX50 Microscope; Olympus, Hamburg, Germany).

The proportionate distribution of the characteristic tissue components like fibrin exudation, macrophages, diffuse or perivascular accumulation of lymphocytes and plasma cells as well as microscopically visible metal particles were semi-quantitatively assessed by a grading score shown in Tables 2 and 3. The grading was performed as previously described (19).

Patch testing

A European standard series of 26 contact allergens including a Co, a Cr and a Ni preparation (Hermal, Reinbek, Germany) supplemented by a metal allergen series was applied on the patients' back. The additional metal allergen series consisted of titanium (Ti) dioxide (0.1%), sodium molybdate (2%) and Mn-chloride (0.5%) (Brial Allergen GmbH, Greven, Germany). Test sites were occluded with Finn chambers for 2 days and responses were evaluated on removal and at 3 days after application and in some cases, also after 1 week. Interpretation of the skin reactions was performed according to the recommendations of the German Contact Dermatitis Research Group, which is in accordance with the International Contact Dermatitis Research Group (ICDR). Test reactions were photo documented.

IgE measurement

Serum samples of the 16 patients were analysed by commercially available enzyme immunoassay (CAP-FEIA®; Phadia, Freiburg, Germany) for the total IgE content and the presence of specific IgE antibody to cat dander, house dust and storage mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), natural rubber latex and grass pollen.

Lymphocyte transformation test

Peripheral blood mononuclear cells (PBMC) were obtained from the heparinized blood by density centrifugation on Ficoll-Hypaque (Phadia, Freiburg, Germany). Cells (1×10^6 /ml) were cultured in RPMI1640 medium (Biochrom, Berlin, Germany) supplemented with heat-inactivated AB-serum, glutamine, antibiotic–antimycotic solution and nonessential amino acids. All cultures were performed in quadruplicate in 96-well plates (Nunc, Roskilde, Denmark). Stimuli were: the pan T-cell mitogen phytohaemagglutinin (PHA) 2.4 µg/ml, tetanus toxoid (TT) 5 µg/ml, NiSO_4 (10^{-4} , 10^{-5} and 10^{-6} M), CrCl_3 (10^{-4} , 10^{-5} and 10^{-6} M), CoCl_2 (10^{-5} , 10^{-6} and 10^{-7} M), MnCl_2 (10^{-5} , 10^{-6} and 10^{-7} M) and Na_2MoO_4 (10^{-5} , 10^{-6} and 10^{-7} M) and culture medium alone as control. After 5 days, cells were pulsed with ^3H thymidine overnight and proliferation was assessed by incorporated radioactivity. The stimulation index (SI) was calculated by the ratio of mean cpm of stimulated to unstimulated cultures.

Results

Histological analysis

Histological examination showed lymphocyte dominated inflammation suggestive of a hypersensitivity reaction in accordance with (19). This included (i) marked diffuse and focal perivascular infiltrates of lymphocytes and plasma cells, sometimes with 'high endothelial venules', (ii) severe fibrin exudation and (iii) frequently, a

Table 1. Overview of patients data characteristics and results of PT, LTT, histomorphology and assessment of correlation between PT/LTT and histomorphology (grading criteria are explained in Table 2)

Patient, age (year), sex	Type of implant	Personal allergological history	Serum IgE	Patch test reactivity to†	LTT reactivity to metals	Histological characteristics					Rating (perivascular and differential lymphocytic and macrophage reaction and fibrin exudation)	Correlation between PT/LTT and morphological reaction
						Ly_p	Ly_d	Ma	Fi	Me		
GT, 78, f	C: Fitek cl S: TCM cl	R	tlgE: 23.8 kU/l slgE: negative	Co	Cr, Mo	##	####	####	#	####	Strong	Yes
FF, 72, m	C: Alloclassic cl S: Alloclassic cl	U	tlgE: 295 kU/l slgE: D.p., D.f.	Negative	Ni, Cr, Co, Mo, Mn	#	#	#	/	#	Slight	Yes, LTT only
FE, 60, f	C: Fitek cl S: Wagner Konus cl	None	tlgE: 175 kU/l slgE: negative	Co, Ni, Cr	Ni	##	###	###	##	#	Strong	Yes
HU, 62, m	C: ACA cl S: Alloclassic cl	Not done	tlgE: 18.5 kU/l slgE: negative	Negative	Negative	##	##	##	#	##	Moderate	No
EW, 83, m	C: Alloclassic CSF cl S: Alloclassic SL cl	None	tlgE: 16.2 kU/l slgE: negative	Negative	Negative	##	/	####	#	#	Moderate	No
SR, 74, m	C: Alloclassic CSF cl S: Alloclassic SL cl	None	tlgE: 5.13 kU/l slgE: negative	Negative	Ni, Co	##	#	#	##	#	Moderate	Yes, LTT only
LH, 65, m	C: Pyramid cl S: DSP cl	None	tlgE: 595 kU/l slgE: D.p., D.f., G1, G2, NL,K	Cr, Co	Ni, Co	####	##	##	##	#	Strong	Yes
ZG, 67, m	C: Alloclassic CSF cl S: Alloclassic SL cl	A, R	tlgE: 16.1 kU/l slgE: negative	Cr	Ni, Cr, Co, Mo, Mn	##	###	##	/	#	Moderate	Yes
KM, 76, f	C: Alloclassic CSF cl S: Alloclassic SL cl	D, M	tlgE: 30 kU/l slgE: negative	Co, Ni, Cr	Co	#	#	#	#	/	Slight	Yes
BA, 70, f	C: Alloclassic CSF cl S: Alloclassic SL cl	D, M	tlgE: 83.2 kU/l slgE: NL	Cr	Ni, Cr, Co, Mo, Mn	####	###	####	###	/	Very strong	Yes
WK, 72, m	C: Alloclassic CSF cl S: Alloclassic SL cl	E, M, R	tlgE: 241 kU/l slgE: D.p., D.f., G1, G2,	Co, Cr, Mo	Negative	###	###	#	###	#	Strong	Yes, PT only
RM, 68, f	C: Alloclassic CSF cl S: Alloclassic SL cl	B, I	tlgE: 32.3 kU/l slgE: negative	Cr	Cr, Co, Mo, Mn	####	###	###	#	##	Strong	Yes
RK, 70, m	C: Chirulen c S: Weber Permalock c	None	tlgE: 9.27 kU/l slgE: negative	Negative	Negative	###	###	####	##	###	Strong	No
ZU, 63, f	C: Bicon cl S: Zweymüller SLR cl	D, M	tlgE: 22.4 kU/l slgE: negative	Co, Ni, Mn	Ni	##	####	####	###	#	Very strong	Yes
MY, 52, f	C: Müller-Ring c S: Alloclassic SL cl	M	tlgE: 7.86 kU/l slgE: negative	Ni	Negative	##	#	###	#	###	Moderate	Yes, Ni max 1% in alloy, PT only
MG, 70, f	C: Pfannendach cl S: Weber SS c	None, FA	tlgE: 14.7 kU/l slgE: negative	Co	Negative	#	#	#	##	#	Moderate	Yes, PT only

PT, patch testing; LTT, lymphocyte transformation test; C, cup; S, stem; A, allergic asthma; B, bee venom allergy; D, drug hypersensitivity; E, implant associated eczema; FA, atopic disease in family; I, intolerance of dental materials; M, cutaneous metal allergy (e.g. eczema to jewellery, wristwatch...); R, allergic rhinoconjunctivitis; U, urticaria; tlgE, total serum IgE (normal ≤ 100 kU/l); slgE, specific IgE; D.p., *Dermatophagoides pteronyssinus*; D.f., *Dermatophagoides farinae*; G1, G2, grass pollen; K, cat dander, NL, natural latex extract; Ni, Nickel(II)sulphate, Co, Cobalt chloride; Cr, Potassium dichromate; Mn, Manganese chloride; Mo, Sodium molybdate; Ly_p, lymphocytes perivascular; Ly_d, lymphocytes diffuse; Ma, macrophages; Fi, fibrin; Me, Metal particles.

†Irritative patch test reactions are not indicated. /, none; #, few; ##, many; ###, abundant; ####, excessive.

pronounced phagocytic reaction, with droplet-like inclusions in the cytoplasm of the macrophages (Fig. 1). Visible metal particles, however, occurred only in small quantities (Table 4). There were no signs of an infection, such as neutrophilic granulocytes, for example.

All the 16 patients exhibited these histomorphological features to a varying extent, but always suggestive of a hypersensitivity reaction (Table 1). The results of

the semi-quantitative histomorphological analysis are summarized in Table 5.

Patch test reactivity

Among the 16 patients, 11 reacted to one or more of the metals tested. The contact allergic PT reactions to metals are listed in Table 1 together with the overview of the patients' data and in more detail in Table 6. Contact

Table 2. Grading of periprosthetic particle storage and tissue reactions [grading system as previously published (19)]

Grading		
Symbol	Description	Explanation
–	None	No particles microscopically detectable
+	Very few	Isolated phagocytosed particles without significant macrophagic reaction
++	Few	Phagocytosed particles to be found in some spots and/or accumulated perivascularly (in the lymphatics)
+++	Many	Evident accumulation of macrophages with phagocytosed particles (also perivascular in the lymphatics)
++++	Abundant	Tissue loaded with particles, including foreign body granulomas
+++++	Excessive	Tissue overstuffed with particles, dominating the structures everywhere

Table 3. Grading of lymphocytic infiltration per field of view [grading system as previously published (19)]

Grading		Amount per field of view	
Symbol	Description	Cells of diffuse infiltration*	Perivascular infiltrates†
–	None	<10	0
+	Slight	11–30	1–2
++	Moderate	31–50	3–6
+++	Strong	51–100	7–10
++++	Very strong	>100	>10

*Magnification 10 × 40; †Magnification 10 × 4.

allergic reactions to Co were found in 7/16, to Cr in 7/16 and to Ni in 4/16 of the patients. To Mn and Mo, we found one reacting patient each.

Serum IgE levels

To address the question of an atopic background of the patients, the personal and family history of allergic rhinoconjunctivitis, asthma and atopic eczema was obtained. In addition, total IgE and specific IgE to *D. pteronyssinus*, *D. farinae*, grass pollen, natural rubber latex and cat dander were measured in blood samples of the 16 patients. In four patients, elevated total serum IgE (>100 kU/l) was found. Four patients had allergen-specific IgE (3 × to *D. pteronyssinus* and *D. farinae*, 2 × to grass pollen, 2 × to natural rubber latex, 1 × to cat dander; partly more than one reaction/patient). The data are summarized in Table 1.

Lymphocyte reactivity *in vitro*

To evaluate the presence of circulating metal specific T lymphocytes, the proliferative response of PBMC of the 16 patients with revised THR was evaluated in the LTT. Twelve individuals without metal allergy (history and PT-negative) served as control blood donors. In Fig. 2, the proliferation (SI) in response to the different metal preparations and to TT as recall antigen is given. Among the 16 patients with revised THR, enhanced proliferation (SI ≥ 3) was observed in 7/16 to Ni, 7/16 to Co, 5/16 to Cr, 5/16 to Mo and 4/16 to Mn. There was no *in-vitro* hyper-reactivity to the Ti preparation. In summary, 10/16 patients showed *in vitro* T-cellular

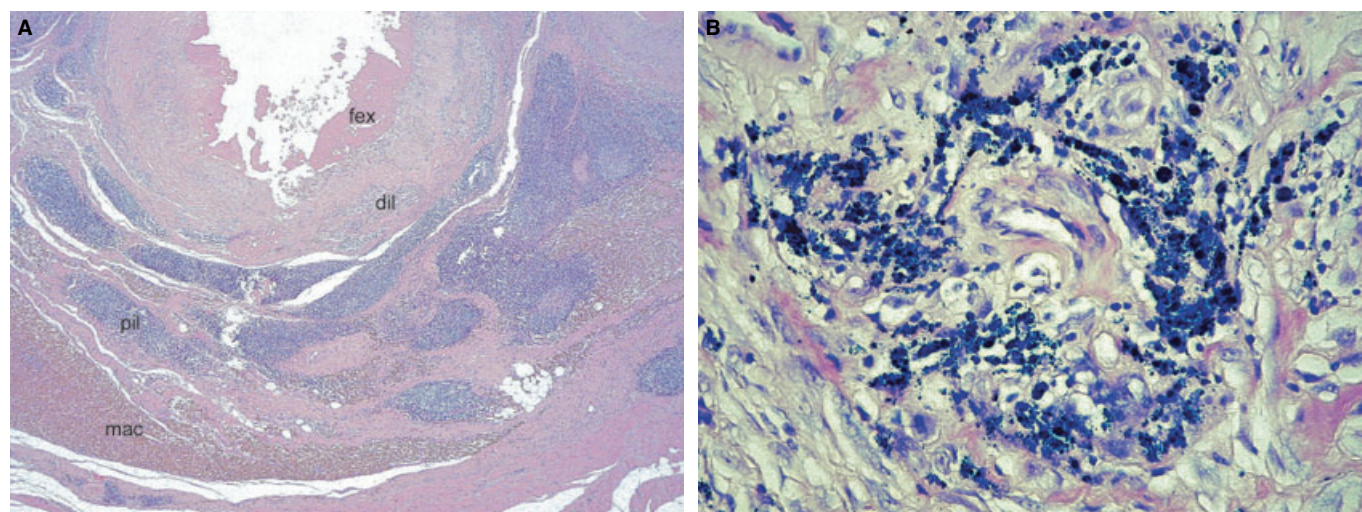


Figure 1. Peri-implant tissue with lymphocyte dominated inflammation. (A) Diffuse (identified in figure by dil) and focal perivascular (pil) infiltrates of lymphocytes and plasma cells, severe fibrin exudation (fex) covering the inner layer and abundant macrophages (mac) in the inner capsule. Paraffin section of capsular tissue, Haematoxylin–Eosin stain, magnification 40-fold (with permission of Orthopaedie im Umbruch, GIT-Verlag Darmstadt, Germany). (B) Perivascular accumulation of macrophages with droplet-like inclusions (homogeneously stained light-blue with varying intensities up to dark blue, nuclei of fibroblasts in homogeneously stained). Paraffin section of capsular tissue, Giemsa stain, magnification 400-fold.

Table 4. Metal content of periprosthetic tissue; three cases of metallosis with two cases of loose implants

Metal content	Number of cases
None	2
Very few	9
Few	2
Many	2
Abundant	1

Table 5. Rating of histomorphology and relation to metal allergy proven by PT and/or metal reactivity in LTT

Overall rating of hypersensitivity in histology	Number of cases	Concomitant DTH rating in histology and metal reactivity in PT and/or LTT, no. of patients (%)	Comment
Slight	2	2/2 (100)	1 with LTT only
Moderate	6	4/6 (66)	2 with PT only 1 with LTT only
Strong	6	5/6 (83)	1 with PT only
Very strong	2	2/2 (100)	

PT, patch testing; LTT, lymphocyte transformation test; DTH, delayed type hypersensitivity.

Table 6. Allergic patch test reactivity to metals in the 16 patients who had undergone revision of THR with metal-on-metal articulation

Contact allergen	Number of reactors	%
Cobalt chloride†	7/16	43.75
Potassium dichromate‡	7/16	43.75
Nickel(II)sulphate§	4/16	25.00
Manganese chloride¶	1/16	6.25
Sodium molybdate††	1/16	6.25
Titanium dioxide‡‡	0/16	0

†1.0% in pet; ‡0.5% in pet; §5.0% in pet; ¶0.5% in H₂O; ††2.0% in pet; ‡‡0.1% in pet.

hyper-reactivity to metals (in part to more than one metal per patient). As shown in Table 1, the LTT reactivity was not always paralleled by positive PT reactions in the same patient.

Association between histomorphology and PT and/or LTT reactivity

We were interested to examine the association between the observed DTH-like histological findings and systemic metal sensitivity, as assessed by PT and LTT. We found a correlation between DTH-indicating histomorphology and the PT- or LTT-reactivity in 13 of the 16 patients (81%) (Table 5). Concomitant evidence of metal sensitivity was seen in eight patients with both, PT and LTT, in three patients with PT only and in another two with LTT only. In only 3/16 patients, the histomorphology was not reflected by positive PT or LTT.

The mean metal content was graded as 1.5 (isolated particles found in some spots) with only three cases exhibiting a metallosis (grading scores 3 or 4; Table 4). Two of these three cases were found upon revision to have loose implants.

Association between reported cutaneous metal allergy reactions and either positive PT and/or positive LTT reactivity

Usually in patients reporting cutaneous metal hypersensitivity (e.g. eczema to jewellery, wristwatch or bracelet), a high rate of metal allergy can be found upon PT, and metal allergy is typically reflected by a history of eczema. An overview of the findings in our 16 patients is given in Tables 1 and 7. In almost one-third (5/16) of the patients, there was a history of pre-existing cutaneous metal allergy/hypersensitivity, e.g. eczema to jewellery or wristwatches, and one of them in addition also had local eczema to the implant. All of these five patients had metal allergy as proven by positive PT reactions and three patients also had positive LTT reaction to metals. In addition, in eight of the 16 patients, metal sensitivity was found by PT and/or LTT – but those eight patients had never observed skin problems upon metal contact. Taken together, in the 16 patients with DTH-like peri-implant reaction, a high rate of metal hypersensitivity was found. However, a large proportion of these patients had no history of metal eczema.

Discussion

Corrosion-derived metal ions or metal wear debris from hip endoprostheses interact with the synovia-like membrane containing macrophages, endothelial cells and immigrating cells like lymphocytes (1, 3, 25). It is well known, that repetitively stimulated macrophages will form foreign-body giant cells in response to particles too large to being phagocytosed. The production of IL-1, TNF- α and IL-6 may trigger osteoclast induction, osteolysis and angiogenesis with the potential of implant loosening (26–28). It seems that foreign body reaction is typically active in aseptic loosening, whereas only some individuals may develop specific immune response against corrosion products like Co, Cr or Ni ions. Nickel or Co as such, but also macrophage-derived cytokines induce vascular adhesion molecules and further recruit monocytes and leucocytes from the circulating blood (29). In the case of specific immune response, T lymphocytes may be preferentially found around the implant. In several recent studies, a lymphocyte dominated inflammation in periprosthetic tissue retrieved at revision surgery has been described, amongst others in patients with metal-on-metal arthroplasty (16–19). Such patients, in the absence of infection, were claimed to have a DTH-like immunological response to the implanted alloy. In addition to peri-implant lymphocyte dominated

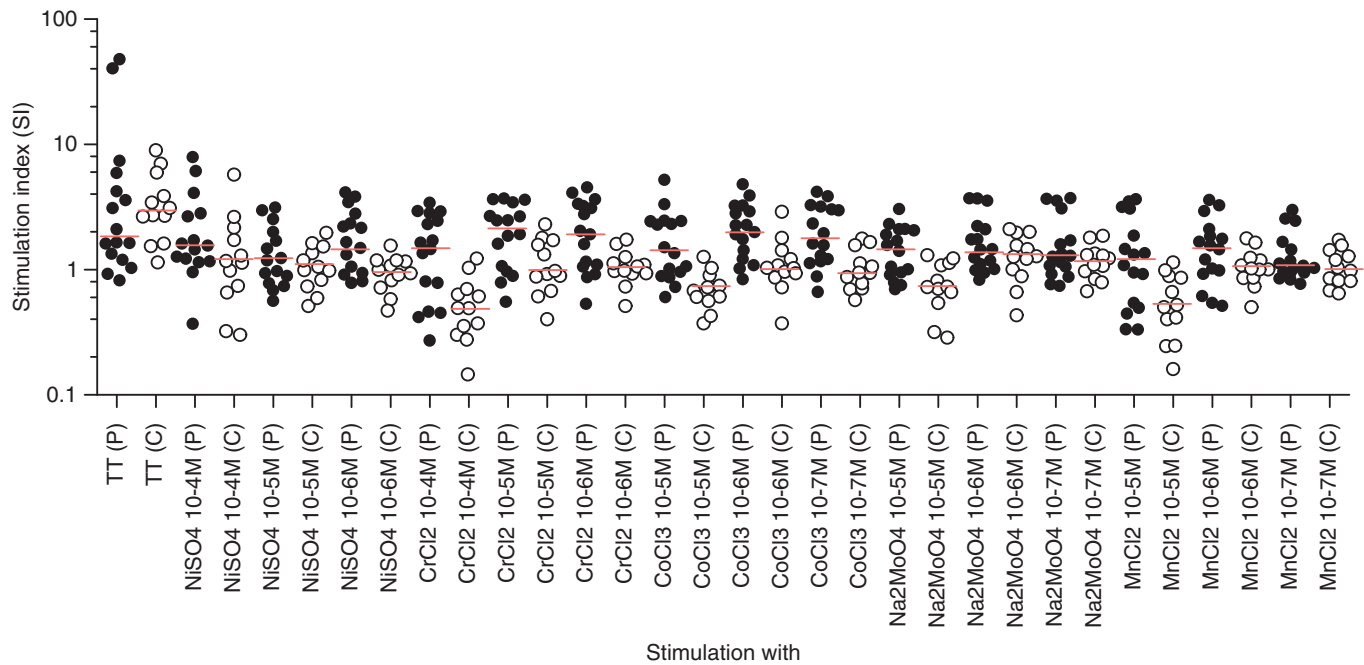


Figure 2. Proliferative response (expressed as SI) of PBMC from 16 patients with revised THR (●) and 12 nonallergic healthy blood donors (○). Partly enhanced proliferative response as indication of metal exposure/sensitization in the THR patients. PBMC, peripheral blood mononuclear cells; THR, total hip replacement; NiSO₄, nickel sulphate; CrCl₂, chromium chloride; CoCl₃, cobalt chloride; Na₂MoO₄, sodium molybdate; MnCl₂, manganese chloride; TT, tetanus toxoid; SI, stimulation index; (–), median.

Table 7. Comparison of detected metal sensitivity (PT and LTT) in 13 of 16 patients with THR revision surgery to the history of pre-existing cutaneous metal intolerance (e.g. eczema) (in the remaining 3/16 patients, there was neither PT/LTT reactivity nor history of pre-existing cutaneous metal sensitivity)

Patient	PT					LTT					Metal reactivity in		History of pre-existing cutaneous metal intolerance† (eczema)
	Co	Cr	Ni	Mo	Mn	Co	Cr	Ni	Mo	Mn	PT	LTT	
RM		#				#	#		#	#	Yes	Yes	No
MG	#										Yes	No	No
GT	#						#		#		Yes	Yes	No
LH	#	#				#		#			Yes	Yes	No
ZG		#				#	#	#	#	#	Yes	Yes	No
FF						#	#	#	#	#	No	Yes	No
FE	#	#	#					#			Yes	Yes	No
SR						#		#			No	Yes	No
BA		#				#	#	#	#	#	Yes	Yes	Pre-existing
WK	#	#		#							Yes	No	Pre-existing and actual‡
ZU	#		#		#			#			Yes	Yes	Pre-existing
MY			#								Yes	No	Pre-existing
KM	#	#	#			#					Yes	Yes	Pre-existing

PT, patch test; LTT, lymphocyte transformation test; Co, Cobalt; Ni, Nickel; Cr, Chromium; Mo, Molybdenum; Mn, Manganese.
†Known (pre-existing) eczema to jewellery and/or wristwatch and/or metal buttons.
‡Actual eczema at the site of implant. #, reactive to.

inflammation, DTH has also been found in intolerance to osteosynthesis material (30). The question of allergic reactions also arose from observations like eczema, impaired wound/fracture healing or even urticaria associated with arthroplasty or osteosynthesis materials (31–35). In these patients, contact allergy to Ni, Co or Cr was described. In early metal-to-metal hip replacement patients, an elevated rate of metal allergy has been

reported (36, 37). Given the rather high prevalence of cutaneous metal sensitization rates, e.g. up to 13% to Ni, 2% to Co and 1% to Cr in the general population (38), the number of metal allergy-related complications in implant bearing patients seems to be low. Allergy diagnostics is not always performed in these patients, and no epidemiological data exist about the incidence of implant-related allergic reactions.

Based on previous observations (19), we performed a combined approach of analysis of periprosthetic tissue, of PT and of assessment of T-lymphocytic reactivity *in vitro*. We had the opportunity to further investigate a series of 16 patients with revised metal-on-metal arthroplasty and lymphocyte dominated peri-implant histomorphology for the presence of systemic metal sensitization. In those patients, the histological examination had shown diffuse and perivascularly oriented lymphocytes, presence of some B cells, high endothelial venules, fibrin exudation, necrosis and macrophages with drop-like inclusions. In 13 of the 16 patients (about 81%), metal sensitivity was found (positive reactions to PT or LTT, or to both). Upon PT, in 11 of the 16 patients (about 69%), a metal allergy was found. There was a high incidence of Co (about 43%), Cr (about 43%) and Ni (25%) allergy in the 16 patients – and there was even one reaction to Mn and one reaction to Mo. These allergy rates are clearly above the incidence rates in the general population and also with respect to uncomplicated implant bearing patients (unpublished data of an ongoing study, P. Thomas, J. Geier). With regard to Mn, Mo and Ti, there is, however, no standardized PT preparation. Thus, the reactions to Mn and Mo have to be seen under this restriction.

The atopy frequency in the 16 individuals, reflected by enhanced IgE serum levels and/or history of atopic diseases like allergic rhinoconjunctivitis, is similar to that in the general population. In central Europe, atopy rates may be up to 25% (39).

When studying metal reactivity in the peripheral blood samples of these 16 patients, many showed enhanced T-lymphocytic proliferation to the metals. To clearly distinguish enhanced reactivity, we had put the cut-off level to a SI ≥ 3 , which is even above that one chosen by several other investigators. We still found elevated reactivity to metals in 10 patients. This elevated response probably reflects a higher number of circulating metal-specific T cells in these individuals and is in accordance with findings of Hallab et al. (40). Lymphocyte transformation test proliferative responses may indicate exposure and sensitization, which, however, should not be overinterpreted as diagnostic step for allergy.

In the present study, five of 16 cases, almost one-third, had a history of pre-existing skin problems upon metal contact and metal allergy proven by PT – supporting the assumption, that metal allergy initially triggered only by skin exposure may eventually also lead to local hypersensitivity in periprosthetic tissue after metal-on-metal arthroplasty. In another eight patients, metal sensitization was found by PT and/or LTT together with peri-implant lymphocytic inflammation but so far no skin problems upon metal contact. These patients might have been sensitized by the implant material. The peri-implant T-lymphocytic infiltrates in the remaining three cases of our study may reflect an immune reaction to it. However, the functional significance of it (e.g. potential hypersensitivity) cannot be answered. Our conclusions may be

supported by (i) the report on a patient with implant failure and periprosthetic Co-specific T-lymphocytic hyper-reactivity (41) and (ii) the observations by Granchi et al., stating that PT was not able to discriminate between stable and failed implants at a single patient level, but that it confirmed a shorter lifespan of THR with metal-on-metal articulation in patients with positive PT (42).

It must be emphasized that, in general, the content of microscopically visible metal particles in the tissues was low, ranging from 'none' to 'few particles to be found only in some spots'. Only three cases showed morphologically the picture of metallosis. These three cases were rated as suggestive for a strong (2) or moderate (1) hypersensitivity reaction, despite one of them not giving metal reactivity both in PT and LTT. Thus, high contents of microscopically visible metal wear particles do not necessarily evoke a strong inflammation nor are they related to a pronounced skin test or LTT reactivity. In addition, our findings of a low content of microscopically visible metal particles did not coincide with a foreign body reaction. This is in accordance with our (HGW) findings in 181 cases of metal-on-metal articulations (unpublished; I. Lang, H.G. Willert). To date, we still do not know the particular conditions under which preferential peri-implant T-cellular inflammation is triggered.

In the patients presented here, the main reasons for revision were pain (50%) and osteolysis (25%). In our patients showing a periprosthetic T-lymphocytic inflammation, a high rate (81%) of metal sensitivity was found. Although the overall allergy-induced failure rate of new metal-on-metal arthroplasty is considered to be low (43) and so far reported case numbers are small, the results of our study underline the advice that pre-operative inquiries about the patient's history should comprise evidences of the allergic disposition. In addition, allergic reactions to Co, Cr or Ni should be included as differential diagnosis in failed metal-on-metal arthroplasty.

Acknowledgments

Cooperation of the following clinicians in preparation of the study is gratefully acknowledged: Dr V. Auersperg, Linz/Austria; Dr R.-J. Döhler and A. Brümmer, Plau-am-See/Germany; Dr D. Simon, Bern/Switzerland. The authors thank Dr C. Rieker for advice and Zimmer GmbH, Winterthur/Switzerland for the funding provided. Monitoring and parts of histopathology were performed by Dr Inge Lang (in completing Prof. Willert's work), and editorial help for preparing the manuscript was given by Dr G. H. Buchhorn, both Göttingen/Germany.

Conflict of interest

The authors received a study grant from Zimmer GmbH, Winterthur, Switzerland, to perform the study. There were no conflicts of interest.

References

1. Black J. Allergic foreign body response. In: Black J, editor. *Biological performance of materials*. 3rd edn. New York: Marcel Decker Inc., 1999:215–232.
2. Goodman SB. Does the immune system play a role in loosening and osteolysis of total joint replacements? *J Long Term Eff Med Implants* 1996;**6**:91–101.
3. Kottinen YT, Zhao D, Beklen A, Ma G, Tkagi M, Kivelä-Rajamäki M et al. The microenvironment around total hip replacement prostheses. *Clin Orthop Relat Res* 2005;**430**:28–38.
4. Willert HG, Semlitsch M. Tissue reactions to plastic and metallic wear products of joint endoprostheses. *Clin Orthop Relat Res* 1996;**333**:4–14.
5. Semlitsch M, Streicher RM, Weber H. The wear behaviour of capsules and heads of CoCrMo casts in long-term implanted all-metal hip prostheses. *Orthopade* 1989;**18**:377–381.
6. Higuchi F, Inoue A, Semlitsch M. Metal-on-metal CoCrMo McKee-Farrar total hip arthroplasty: characteristics from a long-term follow-up study. *Arch Orthop Trauma Surg* 1997;**116**:121–124.
7. Willert HG, Buchhorn GH, Gobel D, Koster G, Schaffner S, Schenk R et al. Wear behavior and histopathology of classic cemented metal on metal hip endoprostheses. *Clin Orthop Relat Res* 1996;**329**:S160–S186.
8. Weber BG. Experience with the Metasul total hip bearing system. *Clin Orthop Relat Res* 1996;**329**:S69–S77.
9. Kim SY, Kyung HS, Ihn JC, Cho MR, Koo KH, Kim CY. Cementless Metasul metal-on metal total hip arthroplasty in patients less than fifty years old. *J Bone Joint Surg Am* 2004;**86-A**:2475–2481.
10. Delaunay CP. Metal-on-metal bearings in cementless primary total hip arthroplasty. *J Arthroplasty* 2004;**19**(8 Suppl. 3):35–40.
11. Dorr LD, Wan Z, Sirianni LE, Boutary M, Chandran S. Fixation and osteolysis with Metasul metal-on-metal articulation. *J Arthroplasty* 2004;**19**:951–955.
12. Jessen N, Nickel A, Schikora K, Buttner-Janzen K. Metal/metal – a new (old) hip bearing system in clinical evaluation. Prospective 7-year follow-up study. *Orthopade* 2004;**33**:594–602 (German).
13. Long WT, Dorr LD, Gendelman V. An American experience with metal-on-metal total hip arthroplasties. A 7-year follow-up study. *J Arthroplasty* 2004;**19**(8 Suppl. 3):29–34.
14. Migaudo H, Jobin A, Chantelot C, Giraud F, Laffargue P, Duquenois A. Cementless metal-on-metal hip arthroplasty in patients less than 50 years of age. comparison with a matched control group using ceramic-on-polyethylene after a minimum 5-year follow-up. *J Arthroplasty* 2004;**19**(8 Suppl. 3):23–28.
15. Rieker CB, Schon R, Kottig P. Development and validation of a second-generation metal-on-metal bearing: laboratory studies and analysis of retrievals. *J Arthroplasty* 2004;**19**(8 Suppl. 3):5–11.
16. Baur W, Hönl W, Willert HG, Schuh A. Pathological findings in tissue surrounding revised metal/metal articulations. *Orthopade* 2005;**34**:225–233 (German).
17. Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP. An unusual lymphocytic perivascular infiltration in tissue around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am* 2005;**87-A**:18–27.
18. Park YS, Moon YW, Lim SJ, Yang JM, Ahn G, Choi YL. Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg Am* 2005;**87**:1515–1521.
19. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am* 2005;**87-A**:28–36.
20. Braathen LR. Studies on human epidermal Langerhans cells – III. Induction of T lymphocyte response to nickel sulphate in sensitized individuals. *Br J Dermatol* 1980;**103**:517–526.
21. Werfel T, Hentschel M, Kapp A, Renz H. Dichotomy of blood- and skin-derived IL-4-producing allergen specific T cells and restricted Vβ repertoire in nickel mediated contact dermatitis. *J Immunol* 1997;**158**:2500–2505.
22. Büdinger L, Hertl M. Immunologic mechanisms in hypersensitivity reactions to metal ions: an overview. *Allergy* 2000;**55**:108–115.
23. Summer B, Sander C, 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.
24. Trautmann A, Akdis M, Brocker EB, Blaser K, Akdis CA. New insights into the role of T cells in atopic dermatitis and allergic contact dermatitis. *Trends Immunol* 2001;**22**:530–532.
25. Goodman SB, Huie P, Song Y, Schurman D, Maloney W, Woolson S et al. Cellular profile and cytokine production at prosthetic interfaces. Study of tissues retrieved from revised hip and knee replacements. *J Bone Joint Surg Br* 1998;**80**:531–539.
26. Jacobs JJ, Sumner DR, Galante JO. Mechanisms of bone loss associated with total hip replacement. *Orthop Clin North Am* 1993;**24**:583–590.
27. Miyazaki K, Trindade MC, Ma T, Goodman SB, Schurman DJ, Smith RL. Periprosthetic osteolysis: induction of vascular endothelial growth factor from human monocyte/macrophages by orthopaedic biomaterial particles. *J Bone Miner Res* 2003;**18**:1573–1583.
28. Looney RJ, Schwarz EM, Boyd A, O'Keefe RJ. Periprosthetic osteolysis: an immunologist's update. *Curr Opin Rheumatol* 2006;**18**:80–87.
29. Goebeler M, Meinardus-Hager G, Roth J, Goerdts S. Nickel chloride and Cobalt chloride, two common contact sensitizers, directly induce expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule (ELAM-1) by endothelial cells. *J Invest Dermatol* 1993;**100**:759–765.
30. Thomas P, Thomas M, Summer B, Naumann T, Sander CA, Przybilla B. Intolerance of osteosynthesis material: evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and TH1-type cytokine expression in the periimplantar tissue. *Allergy* 2000;**55**:969–972.
31. McKenzie AW, Aitken CV, Ridsdill-Smith R. Urticaria after insertion of Smith-Petersen vitallium nail. *Br Med J* 1967;**4**:36.
32. Kubba R, Taylor JS, Marks KE. Cutaneous complications of orthopedic implants. A two-year prospective study. *Arch Dermatol* 1981;**117**:554–560.
33. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001;**83-A**:428–436.
34. Swiontkowski MF, Agel J, Schwappach J, McNair P, Welch M. Cutaneous metal sensitivity in patients with orthopaedic injuries. *J Orthop Trauma* 2001;**15**:86–89.
35. Thomas P. Allergic reactions to implant materials. *Orthopade* 2003;**32**:60–64 (Review, German).
36. Elves MW, Wilson JN, Scales JT, Kemp HB. Incidence of metal sensitivity in patients with total joint replacements. *Br Med J* 1975;**15**:376–378.

37. Benson MK, Goodwin PG, Brostoff J. Metal sensitivity in patients with joint replacement arthroplasties. *Br Med J* 1975;**15**:374–375.
38. Schäfer T, Bohler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B et al. Epidemiology of contact allergy in adults. *Allergy* 2001;**56**:1192–1196.
39. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–743.
40. Hallab NJ, Anderson S, Stafford T, Glant T, Jacobs JJ. Lymphocyte responses in patients with total hip arthroplasty. *J Orthop Res* 2005;**23**:384–391.
41. Schoberl A, Summer B, Jakob K, Barnstorf S, Thomas P. Periimplantar cobalt specific DTH reaction in a patch test negative patient with failure of hip arthroplasty. *J Allergy Clin Immunol* 2004;**113**:250–251.
42. 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**:257–264.
43. Gawkrödger DJ. Metal sensitivities and orthopaedic implants revisited: the potential for metal allergy with the new metal-on-metal joint prostheses. *Br J Dermatol* 2003;**148**:1089–1093.