

ORIGINAL ARTICLE

Metal hypersensitivity in patients with orthopaedic implant complications—A retrospective clinical study

Stefan Furrer¹  | Kathrin Scherer Hofmeier¹ | Leticia Grize^{2,3} | Andreas J. Bircher^{1,3}¹Department of Dermatology, Allergy Unit, University Hospital, Basel, Switzerland²Swiss Tropical and Public Health Institute, Basel, Switzerland³University of Basel, Basel, Switzerland**Correspondence**

Professor Dr A. J. Bircher, Allergy Unit, Department of Dermatology, University Hospital, Petersgraben 4, CH-4031 Basel, Switzerland.

Email: andreas.bircher@unibas.ch

Background: Hypersensitivity to metals as a cause of implant-related complications has been a subject of controversy. Projections indicate an increase in the frequency of joint replacements of between 300% and 600% by the year 2030; therefore, this issue is of considerable interest.**Objective:** To evaluate sensitization to implant materials in patients with implant-related complications, to identify allergens, and to clarify whether hypersensitivity is a relevant cause.**Methods:** Patients with implant-related complications or a positive history of contact allergy and planned total joint replacements referred for allergological investigation between 2004 and 2017 were retrospectively analysed.**Results:** In total, 311 patients were included. A positive patch test reaction to a metal was seen in 64.4% of preoperative patients and in 54.6% of patients with implant-related complications. Common alloy metals such as cobalt, chromium and titanium gave positive reactions in up to 2.9% of patients with implant-related complications. None of the patients with skin changes had a positive patch test reaction to an implant metal.**Conclusion:** Other factors, such as the type of replaced joint and mechanical stress, seem to be more relevant for implant-related complications. Sensitization to metals or other materials seems to rarely play a role, and is overestimated.**KEYWORDS**

implant complications, implant failure, metal allergy, metal hypersensitivity, osteosynthesis, patch test, total joint replacement

1 | INTRODUCTION

The number of total joint arthroplasties (TJAs), especially hip and knee replacements, has considerably increased over the years.^{1,2} Projections predict the frequency of TJAs to further increase by 300% to over 600% by the year 2030.^{3,4} As the number of TJAs increases, the rate of complications may rise. Infections after TJA despite antibiotic prophylaxis occur in approximately 1% to 2% of cases.⁵ Beside infections, other implant-related complications such as malalignment, loosening, skin changes, pain and swelling may occur. One potential cause that has been widely discussed is a hypersensitivity reaction to a metal or bone cement component.^{6–15} According to case reports, allergic reactions to such materials have been rarely described.^{16–30} Larger studies evaluated potential allergens and hypersensitivity prevalences after TJA, and tried to establish general preoperative (PO) and postoperative guidelines in cases of suspected metal

hypersensitivity.^{13,15,31,32} Other diagnostic approaches, for example, cellular in vitro methods (lymphocyte transformation/stimulation or leukocyte migration inhibition tests), were used as the validity of patch tests was questioned.³³ Most authors recommend patch testing in PO patients with a history of contact allergy only,^{33–35} whereas others suggest general screening.³⁶ Therefore, prevalences of sensitization to metal and bone cement components are hugely different between studies.^{12,14,33} Hitherto, the question of whether implant complications occur because of hypersensitivity or vice versa has not been completely answered.³⁷

In this study, the prevalences of sensitization to metals and bone cement components in patients with osteosynthesis (OS) and TJA-related complications were evaluated, potential allergens were identified, and, if possible, the relevance was established. These groups were compared with a PO group with a history of metal contact allergy.

2 | PATIENTS AND METHODS

We retrospectively analysed all patients from 2004 to 2017 who had an allergological work-up at the Allergy Unit of the University Hospital Basel, either following implant-related complications or as a PO evaluation concerning metal hypersensitivity. Informed general consent was obtained, and the study was approved by the local ethics committee. Patients with implant-related complications were referred after infection and malalignment had already been ruled out or seemed unlikely. PO testing was performed in a majority of patients with a clear history of contact allergy to metals, and rarely for other reasons, who were to receive a TJA. Patients with problems regarding dental implants or other medical devices such as stents and pacemakers were excluded. Assessment included a detailed history, inspection of skin, oral mucosa, dental status, and the affected joint, as well as patch testing. The vast majority of patch tests were indicated and read by the same 2 physicians. The history comprised information about former and current symptoms, metal contact allergy, occupational or recreational exposure to metals, previous metal implants, presence of tattoos or piercings, implantation date, type and composition of the implant, and whether the implant was cemented. Symptoms were categorized as "pain", "swelling", "loosening", "skin changes", and "others". Patients could have several symptoms.

2.1 | Patch tests

The European baseline series (Chemotechnique Diagnostics, Vellinge, Sweden; SmartPractice respectively, Almirall Hermal, Reinbek, Germany), an extended metal series (Table 1) (containing frequent metal allergens, common alloy metals of implants and also other metals rarely eliciting contact allergy, such as palladium ([Pd], rhodium, and mercury [Hg], which are not present in orthopaedic implant alloys) and bone cement components (Table 2) were tested in IQ Chambers (Chemotechnique Diagnostics). According to the standardized approach in our clinic, all patients were tested with all patch test series, including bone cement components, irrespective of indication. Patch tests were applied for 2 days on the patient's upper back. The first reading was performed on day (D) 2, and the second reading was performed between D3 and D6. Test reactions were rated according to ICDRG/ESCD guidelines for patch testing.^{38,39}

2.2 | Statistical analysis

One examination per patient was analysed; the most recent examination was considered if the patient had had >1 consultation during the study time. Five groups were defined: PO, OS, hip total prosthesis (HTP), knee total prosthesis (KTP), and shoulder total prosthesis (STP). Patient characteristics and the results of allergy testing were evaluated by comparing results between different groups, and comparing the implant groups OS, HTP, KTP and STP with the PO group. Comparisons of categorical variables among groups were performed with Fisher's exact test or the χ^2 test, as applicable. For comparisons of continuous variables, the Mann-Whitney *U* test was used. The statistical significance level was set at $P < .05$.

TABLE 1 Metal compounds used for patch testing

Metals	Concentration (%)	Vehicle
Aluminium ^a	100	
Aluminium chloride ^a	2	pet.
Ammonium molybdate tetrahydrate ^b	1	aq.
Calcium titanate ^a	10	pet.
Cobalt chloride ^{b c}	1	pet.
Manganese chloride ^a	2	pet.
Molybdenum ^a	5	pet.
Nickel sulfate ^{b c}	5	pet.
Niobium chloride ^d	1	pet.
Palladium chloride ^e	1	pet.
Potassium dichromate ^{b c}	0.5	pet.
Rhodium chloride ^d	3	pet.
Sodium tetrachloropalladate ^a	3	pet.
Titanium chloride ^a	0.1	aq.
Titanium ^a	10	pet.
Titanium nitride ^a	5	pet.
Titanium oxalate decahydrate ^a	1	pet.
Vanadium metal ^a	5	pet.
Vanadium chloride ^a	1	pet.
Zirconium chloride ^a	1	pet.

^a Chemotechnique Diagnostics (Vellinge, Sweden).

^b AllergEAZE—SmartPractice Europe respectively Almirall Hermal (Reinbek, Germany).

^c From the European baseline series.

^d Produced in-house.

^e Trolab—SmartPractice Europe resp. Almirall Hermal (Reinbek, Germany).

Additionally tested metals are shown in Table S1.

3 | RESULTS

3.1 | Patients

We analysed a total of 311 patients: 220 (70.7%) females and 91 (29.3%) males. The mean age of the whole study population was 63.9 years (95%CI: 52.9–74.9). Seventy-three (23.5%) patients had a PO examination, and 238 (76.5%) patients were suffering from implant-related complications: 175 (73.5%) in the KTP group,

TABLE 2 Patch test substances of bone cement components

Component	Concentration (%)	Vehicle
2-Hydroxyethyl methacrylate	1	pet.
4,4'-Diaminodiphenylmethane	0.5	pet.
Barium sulfate	5	pet.
Benzoyl peroxide	1	pet.
Gentamicin sulfate	20	pet.
Hydroquinone	1	pet.
Methyl methacrylate	2	pet.
N,N-dimethyl-4-toluidine	2	pet.
Zirconium chloride	1	pet.
Palacos bone cement	"as is" ^a	-

AllergEAZE test compounds (SmartPractice Europe resp. Almirall Hermal, Reinbek, Germany),

^a Cured and dried in the form of a flat 10-mm disc.

TABLE 3 Specified symptoms by implant group

	Pain, <i>n</i> (%)	Swelling, <i>n</i> (%)	Skin, <i>n</i> (%)	Loosening, <i>n</i> (%)	Others, <i>n</i> (%)
Any implant (<i>N</i> = 238)	177 (74.4)	81 (34)	26 (10.9)	52 (21.8)	14 (5.9)
HTP (<i>N</i> = 28)	12 (42.9)	3 (10.7)	5 (17.9)	6 (21.4)	3 (10.7)
KTP (<i>N</i> = 175)	151 (86.3)	76 (43.4)	13 (7.4)	40 (22.9)	6 (3.4)
STP (<i>N</i> = 4)	3 (75)	1 (25)	2 (50)	1 (25)	-
Osteosynthesis (<i>N</i> = 31)	11 (35.5)	1 (3.2)	6 (19.3)	5 (16.1)	5 (16.1)

Abbreviations: HTP, hip total prosthesis; KTP, knee total prosthesis; STP, shoulder total prosthesis. For KTP vs HTP, the *P* values are <.0001 for pain and .0007 for swelling.

28 (11.8%) in the HTP group, 4 (1.7%) in the STP group, and 31 (13%) in the OS group. Fifty-eight (79.5%) patients from the PO group and 110 (46.2%) patients with implant-related complications had a history of a previous contact allergy (*P* < .0001). Current symptoms of patients with implants included: pain (177; 74.4%), swelling (81; 34%), loosening (52; 21.8%), skin changes (26; 10.9%), and "other" symptoms or findings (14; 5.9%) (Table 3). There were no relevant findings regarding oral and dental status. On the basis of an implant pass or other sources, the implant type was identifiable in 166 (69.7%) cases and the corresponding alloy in 134 (56.3%). Joint prostheses were cemented in 179 (75%) patients (HTP, 20 [71.4%]; KTP, 157 [89.7%]; and STP, 2 [50%]). The available information on metal components is shown in Table 4.

3.2 | Patch test results

The highest prevalence of positive reactions was observed for Pd (tested as sodium tetrachloropalladate) (*n* = 62, 23.3%), followed by nickel sulfate (*n* = 51, 16.4%), benzoyl peroxide (*n* = 36, 11.6%), rhodium chloride (*n* = 27, 8.3%), and Pd (tested as PdCl₂) (*n* = 24, 7.7%). Thirty-six patients reacted positively to nickel sulfate and Pd, tested either as sodium tetrachloropalladate (*n* = 15) or palladium chloride (*n* = 3), or both (*n* = 18). In contrast, titanium (Ti), for example, which is a frequently used alloy metal in OS and some KTPs and HTPs, tested in 5 different compounds, always gave negative results. Only 12 patients (15.6%) with Ti-containing implants showed a positive patch test reaction to nickel sulfate. Comparisons between the 2 largest groups, patients with KTPs and HTPs, respectively, showed no significant difference regarding sensitization prevalences. The complete

patch test results for metals and bone cement components are shown in Table 5.

4 | DISCUSSION

4.1 | PO group

As expected, the PO group had the highest proportion of positive patch test reactions to metals (64.4%). This is not surprising, as one of the major reasons for a PO allergological work-up was a history of metal contact allergy. It has to be kept in mind, however, that PO patients are, on average, of younger age, and sensitization prevalences vary with age.¹¹ As expected, Pd and nickel (Ni) were most often positive. In the general population, the most frequent metal contact allergen is Ni, followed by cobalt (Co) and chromium (Cr).^{40,41} Previous studies found hypersensitivity to any of those metals in approximately 10% to 15% of the general population and in 12% to 23% of PO patients with a planned HTP.^{14,33} However, Pd is not included in the baseline series, making a comparison difficult. The high number of positive test reactions to Pd can partly be explained by cross-reactivity to Ni,^{42,43} a high proportion of which has been observed in previous studies in our clinic.⁴⁴

Currently used metal alloys mainly consist of Co-Cr-molybdenum (Mo) (60% Co, 30% Cr, and 7% Mo), Ti-vanadium (V)-aluminium (Al) (86%-90% Ti, 6% Al, and 4% V), or Ti-Al-niobium (Nb) (86%-90% Ti, 6% Al, and 7% Nb), and contain traces of Ni (<1%).^{15,45,46} In our study, positive patch test reactions to 1 of these alloy metals were rare. Nevertheless, PO examination may help in deciding which alloy

TABLE 4 Implant metal compositions

	Any implant (<i>N</i> = 134), <i>n</i> (%)	HTP (<i>N</i> = 17), <i>n</i> (%)	KTP (<i>N</i> = 91), <i>n</i> (%)	STP (<i>N</i> = 1), <i>n</i> (%)	OS (<i>N</i> = 25), <i>n</i> (%)
Cobalt	102 (76.1%)	13 (76.5)	84 (92.3)	1	4 (16)
Chromium	105 (78.4)	12 (70.6)	84 (92.3)	1	8 (32)
Molybdenum	94 (70.1)	10 (58.8)	79 (86.8)	1	4 (16)
Nickel	11 (8.2)	2 (11.8)	2 (2.2)	-	7 (28)
Titanium	75 (56)	12 (70.6)	42 (46.2)	1	20 (80)
Aluminium	23 (17.2)	4 (23.5)	15 (16.5)	1	3 (12)
Vanadium	18 (13.4)	2 (11.8)	15 (16.5)	1	-
Iron	4 (3)	-	-	-	4 (16)
Manganese	1 (0.7)	-	-	-	1 (4)
Niobium	7 (5.2)	3 (17.6)	2 (2.2)	-	2 (8)
Zirconium	2 (1.5)	-	2 (2.2)	-	-

Abbreviations: HTP, hip total prosthesis; KTP, knee total prosthesis; OS, osteosynthesis; STP, shoulder total prosthesis. Metals were considered only if the implant contained >1%.

TABLE 5 Patch test reactions to orthopaedic implant materials

	Concentration (%) ^a	PO (N = 73), n (%)	Patients with implants (N = 238), n (%)	PO vs patients with implants (P value)	OS (N = 31), n (%)	KTP (N = 175), n (%)	HTP (N = 28), n (%)	KTP vs HTP (P value)
Any metal		47 (64.4)	130 (54.6)	.14	11 (35.5)	99 (56.7)	14 (50)	.52
Nickel sulfate	5	25 (34.2)	26 (10.9)	<.0001	6 (19.4)	18 (10.3)	2 (7.1)	>.99
Cobalt chloride	1	11 (15.1)	7 (2.9)	.0001	3 (9.7)	4 (2.3)	0	>.99
Potassium dichromate	0.5	2 (2.7)	4 (1.7)	.63	1 (3.2)	3 (1.7)	0	>.99
Molybdenum	5	0	0	-	0	0	0	-
Ammonium molybdate tetrahydrate	1 (aq.)	0	0	-	0	0	0	-
Titanium	10	0	0	-	0	0	0	-
Titanium chloride	0.1 (aq.)	0	0	-	0	0	0	-
Titanium nitride	5	0	0	-	0	0	0	-
Titanium oxalate decahydrate	1	0	0	-	0	0	0	-
Calcium titanate	10	0	0	-	0	0	0	-
Aluminium	100	0	0	-	0	0	0	-
Aluminium chloride	2	0	1 (0.4)	>.99	0	0	1 (3.6)	.14
Vanadium metal	5	0	1 (0.4)	>.99	0	1 (0.6)	0	>.99
Vanadium chloride	1	1 (1.4)	5 (2.1)	>.99	1 (3.2)	3 (1.7)	1 (3.6)	.45
Niobium chloride	1	1 (1.4)	1 (0.4)	.42	1 (3.2)	0	0	-
Manganese chloride	2	2 (2.7)	14 (5.9)	.38	4 (12.9)	7 (4)	2 (7.1)	.36
Zirconium chloride	1	0	0	-	0	0	0	-
Any bone cement component		8 (11)	32 (13.4)	.46	3 (9.7)	22 (12.6)	6 (21.4)	.21
Benzoyl peroxide	1	5 (6.8)	31 (13)	.32	3 (9.7)	22 (12.6)	5 (17.9)	.44
Gentamicin	20	0	2 (0.84)	.99	0	2 (1.2)	0	>.99

Abbreviations: HTP, hip total prosthesis; KTP, knee total prosthesis; OS, osteosynthesis; PO, preoperative. Positive patch test reactions in PO patients and in patients with implant-related complications plus comparison of the 2 groups, and positive patch test reactions in OS patients as well as KTP and HTP patients plus comparison. Allergens in pet., except where indicated otherwise.

^a The vehicle was pet., unless specified otherwise.

to choose. It is a common notion that a PO examination is helpful and is indicated only in patients with a history of contact allergy or past implant-related complications that were not clearly attributable to infection or malalignment.^{10,33,35} Frigerio et al patch tested 100 patients prior to an HTP or KTP, irrespective of a history of contact allergy, in contrast to our study, in which preoperatively tested patients had to have a history of metal sensitivity.¹⁵ Twenty-three per cent of the patients of Frigerio et al had a positive patch test reaction; that is, approximately three quarters of his patients underwent the complete test process, resulting in unnecessary costs. As in previous studies, this suggests that a negative history of contact allergy and negative patch test results have good concordance.^{47,48} Therefore, with the much higher proportion of positive results and the low prevalence of relevant PO positive patch test reactions in our study, we suggest that only patients with a clear history of contact allergy to metals should be patch tested.

4.2 | OS implant group

Patients with OSs are generally younger than those with TJAs. OSs often consist of different alloy metals, are not cemented, and are typically removed after a certain time period. Formerly, OSs consisted mostly of stainless steel, with high proportions of Ni, Cr, and iron.⁴⁹

Since the mid-1980s, Ti has become more important.^{50,51} Therefore 80% of the OSs in our patients were made of Ti alloys. Only very few case reports have suggested allergic reactions to Ti,⁵²⁻⁵⁸ and we observed no positive reactions to Ti compounds in these groups. However, it was reported that a similar inflammatory tissue reaction was triggered by metallic stainless steel and Ti particles.⁵⁹ However, alloy metals other than Ti were not ruled out as the causes of these reactions. Schuh et al have claimed that Ni traces in Ti implants may provoke an allergic reaction.⁶⁰ Our results do not support this assumption; only 15.5% of the patients with a Ti-containing implant had a positive patch test reaction to Ni. This proportion is even lower than the sensitization prevalence in the general population.⁶¹ Although our number of patients is small, we assume that the vast majority of OS-related complications, with infection and loosening ruled out, are not caused by an allergic reaction.

4.3 | Prosthesis implant groups

With only 4 patients, the STP group is too small to allow any further conclusions. In our study, the KTP group was the largest group. Most of these patients (86.4%) suffered from pain, representing the highest proportion among all groups. Conversely, skin changes constituted the rarest complaint. Interestingly, although HTPs are performed far

more often than KTPs, the number of patients with implant-related complications is significantly lower.⁴ In the HTP group, symptoms were more evenly distributed, and pain, especially, seemed to occur less frequently. In our cohort, only 28 patients had an allergological work-up because of a suspected hypersensitivity reaction after receiving an HTP. The proportions of positive Ni, Co and Cr test reactions in our study (1%-10%) were well below the 25% and 60% in patients with well-functioning and malfunctioning prostheses, respectively, in a review of studies using different test methods (patch tests, lymphocyte migration test, or lymphocyte transformation test) published by Hallab et al.¹⁴ The proportion of patients sensitized to Ni in our study was even lower than the sensitization prevalence in the general population.^{61,62}

4.4 | General considerations

Only a few studies have compared patch test results between PO and postoperative patients.^{35,63} The prevalence of positive patch test reactions to any metal was similar to ours, with higher proportions in postoperative patients than in our study. However, the individual share of positive test reactions for each metal was higher in both PO and postoperative patients in the study of Atanaskova Mesinkovska et al, whereas Reed et al did not observe any positive reactions to a prosthesis component in postoperative patients.^{35,63}

Allergic reactions to metal alloys obviously occur in individual patients, as shown by a considerable number of case reports.^{16-20,23-26,28} Sterile inflammation and loosening resulting from metal allergy may lead to pain and swelling. Allergic contact dermatitis was rarely observed in our OS group. In TJA patients, skin lesions were mostly attributable to oedema, or were non-specific eczema. As mentioned above, current joint prostheses contain mainly Co-Cr-Mo or Ti-Al-V or, instead of Al, Nb alloys with traces of Ni.^{15,45} In our study, the prevalence of sensitization to 1 of the main alloy metals was 2.9%, at most. Like that of Ni, the prevalence of Co and Cr allergy in our study was lower than in the general patch tested population: 6% for Co, and 3.8% for Cr.⁶¹ Furthermore, there were no positive patch test reactions to Ti or Mo, and, for the other metals, there was no significant difference between KTPs and HTPs.

Hip and knee joints differ considerably regarding anatomy, function, and mechanical stress affecting the joint. Both the vastly different number of patients and the fact that the sensitization prevalences of the 2 groups were similar led us to assume that allergic reactions are not important in causing complications. In addition, some patients concurrently had 2 or, rarely, 3 TJAs, whereas only 1, typically the KTP, caused problems. We therefore hypothesize that the type and characteristics of the affected joint and, for example, mechanical forces are more likely explanations for most signs and symptoms related to TJA.

Bone cement components have been discussed as causing relevant hypersensitivity reactions^{29,64-66}. Several case reports have suggested an association with benzoyl peroxide and the antibiotic gentamicin.^{21,22,27-29} The majority of patients in our study had a cemented prosthesis, and HTP patients had a positive patch test reaction to a bone cement component more often than KTP patients, although the difference did not reach statistical significance.

Our prevalence of sensitization to any bone cement component (13.4%) was clearly lower than that, for example, in a study by Eben et al (31.8%).⁶⁶ Although all cement components were tested, almost all of our positive reactions (13%) were to benzoyl peroxide, which is clearly a higher rate than in other studies.^{64,66} The validity of patch test results for benzoyl peroxide has been discussed for years. For example, Ockenfels et al mentioned the frequent difficulty of differentiating between irritant and allergic reactions, and therefore the uncertainty about the validity of results.⁶⁷ For this reason, we simultaneously tested benzoyl peroxide in 2 different chambers, making our results more robust. In contrast to our results, Thomas et al have observed sensitization to gentamicin in 17% of patients after they have received a cemented TJA.⁶⁴ On the basis of these observations and a non-significant difference between PO and postoperative positive patch test reactions to bone cement components, we assume that relevant contact allergy to bone cement components is also rare. However, in a few patients, replacement of a cemented prosthesis with a non-cemented model resulted in an important reduction in symptoms and the prevention of further loosening.^{21,22,27,29}

Because of our standardized approach of testing all patients with implant-related complications, excluding dental issues, with all metals and bone cement components, we observed a considerable number of positive patch test reactions to compounds not present in orthopaedic implants. For instance, we found rather high numbers of positive patch test reactions to rhodium chloride and manganese chloride, as well as to vanadium chloride, although the prevalence of sensitization to vanadium metal was lower. A recent study by Shallcross et al showed high numbers of irritant patch test reactions to manganese chloride, even in low concentrations.⁶⁸ The use of manganese oxide resulted in fewer irritant reactions. The authors suggested biochemical reasons (eg, oxidation state) for irritant reactions. Hypothetically, in some metals, the applied anion chloride, for example, rhodium or vanadium chloride, may often induce an irritant skin reaction, rather than the metal cation itself. In contrast, palladium chloride gave positive reactions less often than sodium tetrachloropalladate, a metal for which the test agent and concentration have been recently studied in more detail, and tetrachloropalladate was recommended as a more suitable test compound. In our opinion, such detailed evaluations should also be performed with metals for which no such studies exist, for example, Ti, V, Nb, manganese, Mo and zirconium compounds, to improve test conditions.

Cross-reactivity between Pd and Ni was shown in several studies.^{42,43,69} In most of those studies, palladium chloride was used for patch testing. Our results also support the theory of cross-reactivity between Pd and Ni, as 70.6% ($n = 36$) of the patients with a positive patch test reaction to Ni also had a positive patch test reaction to at least 1 Pd compound. The association seems to be higher for palladium chloride, as 21 of 27 patients (77.8%) with a positive patch test reaction to palladium chloride also had a positive patch test reaction to Ni, whereas only 33 of 61 patients (54.1%) with a positive patch test reaction to tetrachloropalladate also had a positive patch test reaction to Ni. It has also been shown in other studies that sodium tetrachloropalladate is more often positive, and therefore more sensitive, than palladium chloride, and sensitization prevalences similar to those for nickel sulfate were found.⁷⁰⁻⁷² The prevalences in postoperative

patients are similar to those found by Muris et al; however, PO patients had much higher prevalences.⁷² In contrast to the findings of Muris et al, in both groups sodium tetrachloropalladate was more often positive than nickel sulfate. As mentioned above, we noticed similar characteristics in former studies from our department.⁴⁴ A reason might be the use of a 3% concentration, as some studies showed a significantly higher number of irritant reactions than with a 2% concentration of tetrachloropalladate.⁷²

4.5 | Strengths and limitations

We analysed >300 patients with different implants, and we performed testing with a large series of metals and bone cement components. Although the usefulness of patch tests has been challenged in several studies, patch tests are still the gold standard for identifying contact allergy, and still constitute the best way to identify contact sensitization to metals.^{7,14,73–75} Nevertheless, except for Ni, Cr, and Co, as well as, for example, e.g. Hg, gold, and Pd, most test preparations for alloy metal allergens are not yet sufficiently validated. For our patch tests, we used metal salt preparations mostly from commercial providers, which have been also used in other studies.^{15,31} The interpretation of patch test results depends greatly on the examiner, and readings and interpretation have to be carefully performed. Our readings were performed by the same experienced dermato-allergologists, making interindividual differences less likely. Depending on the availability of the patient, the second reading was performed between D3 and D6. This may have influenced our results, because some late reactions may typically occur beyond D3. However, the majority of the patients had a late reading beyond D3. Regarding the composition of the implants, surprisingly, we often were not able to identify the exact alloys of all implants, as many patients did not receive an implant pass, especially if the TJA had been performed in earlier years. For most cases, we were not able to obtain a follow-up and an outcome, or to perform patch tests after a surgical intervention. Such information, however, is crucial for an overall validation of this test procedure.

5 | CONCLUSIONS

Metal or bone cement component hypersensitivity in patients with implant-related complications may be relevant in individual cases, as shown by many case reports. On the basis of our observations, however, in the vast majority it does not seem to be pertinent, and we therefore assume that the role of delayed hypersensitivity to alloy metals as a cause of implant-related complications may be overestimated. For instance, none of the patients with skin changes had a relevant patch test reaction. Patients with other implant-related complications had a very low prevalence of sensitization to any alloy metal, so the replacement of a TJA had to be considered only rarely. Replacement of a prosthesis was always recommended on the basis of the entire individual situation, and not just on the basis of a positive patch test reaction. Patients, for example, with a positive patch test reaction to Cr or Co were advised to use another metal alloy. As expected, PO patients with a history of metal sensitivity had higher

prevalences of sensitization to Ni and Pd, most likely because of selection bias.

With only few relevant positive patch test reactions in postoperative patients, we do not recommend a general allergological examination in patients with implant-related complications, particularly when only the baseline series is used. However, in patients with a high suspicion of potentially material-related problems, an extensive evaluation is advisable. On the other hand, routine PO testing should be performed only in patients with a positive history of contact allergy.

Several currently unresolved issues remain:

1. The exact composition of the implants was often not available. Hence, a complete assessment was not possible; this problem needs to be solved by providing every patient with detailed information on the type and composition of the prosthesis in an “implant passport”.
2. Establishment of the relevance of a positive patch test reaction in implant patients is particularly challenging; patients with TJA and contact sensitization to implant metals may not have any complaints or complications.
3. There is a lack of standardization and validation of patch test preparations with metals such as Ti, V, and Nb, which rarely elicit delayed hypersensitivity. This may lead to an overestimation of the irritant potential of metals, and an underestimation when the optimal test conditions are not established. Additionally, it makes comparison among studies difficult.
4. Other mechanisms that cannot be diagnosed with patch tests, for example, activation of innate immune pathways or foreign body reactions, may play a role in implant failure.

With regard to the increasing number of patients in need of a joint replacement, these issues need to be addressed and clarified.

Conflict of interest

The authors declare no potential conflict of interests.

ORCID

Stefan Furrer  <http://orcid.org/0000-0002-1468-6889>

REFERENCES

1. Patel A, Pavlou G, Mújica-Mota RE, Toms AD. The epidemiology of revision total knee and hip arthroplasty in England and Wales: a comparative analysis with projections for the United States. A study using the National Joint Registry dataset. *Bone Joint J.* 2015;97-B: 1076-1081.
2. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of total hip and knee replacement in the United States. *J Bone Joint Surg Am.* 2015;97:1386-1397.
3. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am.* 2007;89:780-785.
4. Otten R, van Roermund PM, Picavet HS. [Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030]. *Ned Tijdschr Geneesk.* 2010;154: A1534.
5. Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of

- periprosthetic infection than cefazolin. *Clin Orthop Relat Res*. 2017; 475:1767-1774.
6. 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*. 2006;77:257-264.
 7. Schalock PC, Menné T, Johansen JD, et al. Hypersensitivity reactions to metallic implants—diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*. 2012;66:4-19.
 8. Roberts TT, Haines CM, Uhl RL. Allergic or hypersensitivity reactions to orthopaedic implants. *J Am Acad Orthop Surg*. 2017;25:693-702.
 9. Faschingbauer M, Renner L, Boettner F. Allergy in total knee replacement. Does it exist? *HSS J*. 2017;13:12-19.
 10. Wawrzynski J, Gil JA, Goodman AD, Waryasz GR. Hypersensitivity to orthopedic implants: a review of the literature. *Rheumatol Ther*. 2017; 4:45-56.
 11. Thyssen JP, Linneberg A, Menné T, Johansen JD. The epidemiology of contact allergy in the general population—prevalence and main findings. *Contact Dermatitis*. 2007;57:287-299.
 12. Teo WZW, Schalock PC. Metal hypersensitivity reactions to orthopedic implants. *Dermatol Ther (Heidelberg)*. 2017;7:53-64.
 13. Mitchelson AJ, Wilson CJ, Mihalko WM, et al. Biomaterial hypersensitivity: is it real? Supportive evidence and approach considerations for metal allergic patients following total knee arthroplasty. *Biomed Res Int*. 2015;2015:137287.
 14. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am*. 2001;83-A:428-436.
 15. Frigerio E, Pigatto PD, Guzzi G, Altomare G. Metal sensitivity in patients with orthopaedic implants: a prospective study. *Contact Dermatitis*. 2011;64:273-279.
 16. Verma SB, Mody B, Gawkrödger DJ. Dermatitis on the knee following knee replacement: a minority of cases show contact allergy to chromate, cobalt or nickel but a causal association is unproven. *Contact Dermatitis*. 2006;54:228-229.
 17. Thomsen M, Rozak M, Thomas P. Pain in a chromium-allergic patient with total knee arthroplasty: disappearance of symptoms after revision with a special surface-coated TKA—a case report. *Acta Orthop*. 2011;82:386-388.
 18. Thomas P, Summer B, Sander CA, Przybilla B, Thomas M, Naumann T. Intolerance of osteosynthesis material: evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and TH1-type cytokine expression in the peri-implantar tissue. *Allergy*. 2000;55: 969-972.
 19. Thienpont E, Berger Y. No allergic reaction after TKA in a chrome-cobalt-nickel-sensitive patient: case report and review of the literature. *Knee Surg Sports Traumatol Arthrosc*. 2013;21:636-640.
 20. Stathopoulos IP, Andrianopoulos N, Paschaloglou D, Tsarouchas I. Revision total knee arthroplasty due to bone cement and metal hypersensitivity. *Arch Orthop Trauma Surg*. 2017;137:267-271.
 21. Schuh A, Thomas P, Reinhold R, et al. [Allergic reaction to components of bone cement after total knee arthroplasty]. *Zentralbl Chir*. 2006; 131:429-431.
 22. Richter-Hintz D, Rieker J, Rauch L, Homey B. [Sensitivity to constituents of bone cement in a patient with joint prosthesis]. *Hautarzt*. 2004;55:987-989.
 23. Perumal V, Alkire M, Swank ML. Unusual presentation of cobalt hypersensitivity in a patient with a metal-on-metal bearing in total hip arthroplasty. *Am J Orthop (Belle Mead NJ)*. 2010;39:E39-E41.
 24. Handa S, Dogra S, Prasad R. Metal sensitivity in a patient with a total knee replacement. *Contact Dermatitis*. 2003;49:259-260.
 25. Gao X, He RX, Yan SG, Wu LD. Dermatitis associated with chromium following total knee arthroplasty. *J Arthroplasty*. 2011;26(665): e13-e16.
 26. Engelhart S, Segal RJ. Allergic reaction to vanadium causes a diffuse eczematous eruption and titanium alloy orthopedic implant failure. *Cutis*. 2017;99:245-249.
 27. Edwards SA, Gardiner J. Hypersensitivity to benzoyl peroxide in a cemented total knee arthroplasty: cement allergy. *J Arthroplasty*. 2007;22(8):1226-1228.
 28. Antony FC, Holden CA. Metal allergy resurfaces in failed hip endoprostheses. *Contact Dermatitis*. 2003;48:49-50.
 29. Bircher AJ, Friederich NF, Seelig W, Scherer K. Allergic complications from orthopaedic joint implants: the role of delayed hypersensitivity to benzoyl peroxide in bone cement. *Contact Dermatitis*. 2012;66: 20-26.
 30. Pacheco KA. Allergy to surgical implants. *J Allergy Clin Immunol Pract*. 2015;3:683-695.
 31. Kręćisz B, Kieć-Świerczyńska M, Chomiczewska-Skóra D. Allergy to orthopedic metal implants—a prospective study. *Int J Occup Med Environ Health*. 2012;25:463-469.
 32. Lützner J, Hartmann A, Dinnebie G, Spornraft-Ragaller P, Hamann C, Kirschner S. Metal hypersensitivity and metal ion levels in patients with coated or uncoated total knee arthroplasty: a randomised controlled study. *Int Orthop*. 2013;37:1925-1931.
 33. Granchi D, Cenni E, Giunti A, Baldini N. Metal hypersensitivity testing in patients undergoing joint replacement: a systematic review. *J Bone Joint Surg Br*. 2012;94:1126-1134.
 34. Thyssen JP, Menné T, Schalock PC, Taylor JS, Maibach HI. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. *Br J Dermatol*. 2011;164:473-478.
 35. Reed KB, Davis MD, Nakamura K, Hanson L, Richardson DM. Retrospective evaluation of patch testing before or after metal device implantation. *Arch Dermatol*. 2008;144:999-1007.
 36. Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. *Biomaterials*. 2005;26:1019-1026.
 37. Basko-Plluska JL, Thyssen JP, Schalock PC. Cutaneous and systemic hypersensitivity reactions to metallic implants. *Dermatitis*. 2011;22: 65-79.
 38. Fregert S, International Contact Dermatitis Research Group. *Manual of contact dermatitis: on behalf of the International Contact Dermatitis Research Group*. edn. ed. Copenhagen: Munksgaard; 1974.
 39. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermatitis*. 2015;73:195-221.
 40. Hallab NJ, Anderson S, Caicedo M, Skipor A, Campbell P, Jacobs JJ. Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty. *J Arthroplasty*. 2004;19:88-93.
 41. Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. *Contact Dermatitis*. 2007;56:10-15.
 42. Hindsén M, Spirén A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. *Contact Dermatitis*. 2005;53:2-8.
 43. Kränke B, Aberer W. Multiple sensitivities to metals. *Contact Dermatitis*. 1996;34:225.
 44. Spoerri I, Scherer K, Michel S, Link S, Bircher AJ, Heijnen IAFM. Detection of nickel and palladium contact hypersensitivity by a flow cytometric lymphocyte proliferation test. *Allergy*. 2015;70:323-327.
 45. Lons A, Putman S, Pasquier G, Migaud H, Drumez E, Girard J. Metallic ion release after knee prosthesis implantation: a prospective study. *Int Orthop*. 2017;41:2503-2508.
 46. Fellah M, Labaiz M, Assala O, et al. Tribological behavior of Ti-6Al-4V and Ti-6Al-7Nb alloys for total hip prosthesis. *Adv Tribol*. 2014; 2014:13.
 47. Böhm I, Brody M, Bauer R. Comparison of personal history with patch test results in metal allergy. *J Dermatol*. 1997;24:510-513.
 48. Kieffer M. Nickel sensitivity: relationship between history and patch test reaction. *Contact Dermatitis*. 1979;5:398-401.
 49. Thomsen M, Thomas P. [Compatibility and allergies of osteosynthesis materials]. *Unfallchirurg*. 2017;120:116-121.
 50. Mutschler W, Hontzsch D. [Steel or titanium for osteosynthesis?]. *Unfallchirurg*. 2017;120:94-95.
 51. Gerber H, Perren SM. Evaluation of tissue compatibility of in vitro cultures of embryonic bone. In: edition 1st, Winter GD, Leray JL, de Groot K, eds. *Evaluation of Biomaterials*. London, England: John Wiley & Sons Ltd; 1980:307-314.
 52. Basketter DA, Whittle E, Monk B. Possible allergy to complex titanium salt. *Contact Dermatitis*. 2000;42:310-311.
 53. Bircher AJ, Stern WB. Allergic contact dermatitis from "titanium" spectacle frames. *Contact Dermatitis*. 2001;45:244-245.

54. Breton JL, Louis JM, Garnier G. [Asthma caused by hard metals: responsibility of titanium]. *Presse Med.* 1992;21:997.
55. Lalor PA, Revell PA, Gray AB, et al. Sensitivity to titanium. A cause of implant failure? *J Bone Joint Surg Br.* 1991;73:25-28.
56. Matthew I, Frame JW. Allergic responses to titanium. *J Oral Maxillofac Surg.* 1998;56:1466-1467.
57. Thewes M, Kretschmer R, Gfesser M, et al. Immunohistochemical characterization of the perivascular infiltrate cells in tissues adjacent to stainless steel implants compared with titanium implants. *Arch Orthop Trauma Surg.* 2001;121:223-226.
58. Walsh G, Mitchell JW. Free surface nickel in CE-marked and non-CE-marked spectacle frames. *Ophthalmic Physiol Opt.* 2002;22:166-171.
59. Voggenreiter G, Leiting S, Brauer H, et al. Immuno-inflammatory tissue reaction to stainless-steel and titanium plates used for internal fixation of long bones. *Biomaterials.* 2003;24:247-254.
60. Schuh A, Thomas P, Kachler W, et al. [Allergic potential of titanium implants]. *Orthopäde.* 2005;34:327-8-330-3.
61. Uter W, Amario-Hita JC, Balato A, et al. European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. *J Eur Acad Dermatol Venereol.* 2017;31:1516-1525.
62. Schoeffler A, Waton J, Latarche C, et al. [Changes in the European baseline series from 1981 to 2011 in a French dermatology-allergy centre]. *Ann Dermatol Venereol.* 2013;140:499-509.
63. Atanaskova Mesinkovska N, Tellez A, Molina L, et al. The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants. *Arch Dermatol.* 2012;148:687-693.
64. Thomas P, Schuh A, Eben R, Thomsen M. [Allergy to bone cement components]. *Orthopäde.* 2008;37:117-120.
65. Thomas B, Kulichova D, Wolf R, Summer B, Mahler V, Thomas P. High frequency of contact allergy to implant and bone cement components, in particular gentamicin, in cemented arthroplasty with complications: usefulness of late patch test reading. *Contact Dermatitis.* 2015;73:343-349.
66. Eben R, Dietrich KA, Nerz C, et al. [Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty]. *Dtsch Med Wochenschr.* 2010;135:1418-1422.
67. Ockenfels HM, Uter W, Lessmann H, Schnuch A, Geier J. Patch testing with benzoyl peroxide: reaction profile and interpretation of positive patch test reactions. *Contact Dermatitis.* 2009;61:209-216.
68. Shallcross L, Ritchie S, Harberts E, Tammara A, Gaitens J, Gaspari AA. Manganese oxidation state as a cause of irritant patch test reactions. *Dermatitis.* 2014;25:66-71.
69. Santucci B, Cannistraci C, Cristaudo A, Picardo M. Multiple sensitivities to transition metals: the nickel palladium reactions. *Contact Dermatitis.* 1996;35:283-286.
70. Muris J, Kleverlaan CJ, Feilzer AJ, Rustemeyer T. Sodium tetrachloropalladate (Na₂[PdCl₄]) as an improved test salt for palladium allergy patch testing. *Contact Dermatitis.* 2008;58:42-46.
71. Muris J, Kleverlaan CJ, Rustemeyer T, et al. Sodium tetrachloropalladate for diagnosing palladium sensitization. *Contact Dermatitis.* 2012;67:94-100.
72. Muris J, Goossens A, Gonçalves M, et al. Sensitization to palladium in Europe. *Contact Dermatitis.* 2015;72:11-19.
73. Schalock PC, Thyssen JP. Patch testers' opinions regarding diagnostic criteria for metal hypersensitivity reactions to metallic implants. *Dermatitis.* 2013;24:183-185.
74. Thomas P, Geier J, Dickel H, et al. [Should metal alloy discs be used for patch testing in suspected metal implant intolerance reaction?]. *Orthopäde.* 2015;44:905-908.
75. Thomas P, Geier J, Dickel H, et al. [DKG statement on the use of metal alloy discs for patch testing in suspected intolerance to metal implants]. *J Dtsch Dermatol Ges.* 2015;13:1001-1005.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Furrer S, Scherer Hofmeier K, Grize L, Bircher AJ. Metal hypersensitivity in patients with orthopaedic implant complications—A retrospective clinical study. *Contact Dermatitis.* 2018;1-8. <https://doi.org/10.1111/cod.13032>

Table 6: Additional metals used for patch testing

Tested compound	Concentration (%)	Vehicle
Amalgam ¹	5	pet.
Amalgam alloy ¹	20	pet.
Ammonium hexachloroiridate ¹	0.1	aq.
Ammonium hexachloroplatinate ²	0.1	aq.
Ammonium tetrachloroplatinate ¹	0.25	pet.
Cadmium chloride ³	0.5	pet.
Copper sulfate ¹	2	pet.
Copper oxide ²	5	pet.
Indium ²	1	pet.
Indium sulfate ²	10	aq.
Indium chloride ²	10	aq.
Iridium ²	1	pet.
Iridium chloride trihydrate ²	1	pet.
Iron chloride ²	2	pet.
Lead acetate trihydrate ²	0.5	aq.
Magnesium chloride ⁴	5	pet.
Mercury amide chloride ¹	1	pet.
Mercury ²	0.5	pet.
Mercury chloride ²	0.1	pet.
Potassium dicyanoaurate ¹	0.002	pet.
Ruthenium oxide ⁴	2	pet.
Silver nitrate ²	1	aq.
Sodium thiosulfatoaurate ¹	0.25	pet.
Thiomersal ¹	0.1	pet.
Tin ²	50	pet.
Tin chloride ¹	0.5	pet.
Tungsten ²	5	pet.
Zinc ²	2.5	pet.

¹ allergEAZE - SmartPractice Europe resp. Almirall Hermal (Reinbek, Germany); ² Chemotechnique Diagnostics (Vellinge, Sweden); ³ HAL Allergy Group (Leiden, Netherlands); ⁴ Hospital Pharmacy