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Contact sensitization to iron: A potentially underestimated metal allergen and elicitor of complications in patients with metal implants

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Abstract

Background: Little is known about sensitization to iron (Fe) in private, occupational, and medical settings, particulary implantology.

Objectives: To investigate sensitization to metals, particularly to Fe, both in pre-implant individuals with presumed metal allergy and in patients with suspected metal implant allergy. To further characterize Fe-sensitized individuals.

Methods: Analysis of patch test reactions to an Fe (II) sulfate–containing metal series in 183 consecutive patients (41 pre-implant, 142 metal implant bearers). Test readings were on day (D)2, D3, and D6. Evaluation of questionnaire-aided history of metal reactivity patterns and demographics of Fe reactors.

Results: Metal reactivity in pre-implant/implant/total group was: to nickel 39%/30%/32%; to cobalt 17%/15%/15%; and to chromium 7%/13%/11%. Co-sensitizations cobalt/nickel (19/58) and cobalt/chromium (11/21) were significant at $P < .001$; co-sensitizations Fe/nickel (4/10) and chromium/knee arthroplasty (11/73) at $P = .03$. Ten of 183 (5.5%) reacted to Fe (2 of 41 pre-implant patients, 8 of 142 implant bearers), with 10 reacting only on D6. Fe reactivity was highest in complicated knee arthroplasty (7/73). Further peculiarities of Fe reactors included frequent isolated Fe reactivity (6/10), occupational metal exposure (7/10), previous (par)enteral Fe substitution (6/10).

Conclusions: The 5.5% prevalence of Fe reactions suggests a potentially underestimated role of this metal allergen in general and in implant bearers. The latter also shows a distinct metal sensitization pattern.

KEYWORDS
chromium, cobalt - delayed type sensitization - allergy, knee arthroplasty, metal implant, metals - iron, nickel

1 | INTRODUCTION

Iron (Fe) is a typical constituent of metal-containing industrial products—steel alloys in particular.[1,2] In addition, Fe-oxide pigments are components of tattoo inks and permanent makeup (PMU).[3,4] Accordingly, exposure to Fe may occur during manufacturing processes, or through contact with products in private or work-related environments. However, for many years, contact allergy to Fe has been reported only sparsely both upon occupational exposure or in daily life.[5] The few case reports on Fe causing occupational allergic contact dermatitis concerned enamellers, toolmakers, or steel welders.[6-8] The following statement from 1996 "*iron does not actually seem to play a role as a contact allergen*"[9] seemed to remain valid, also in view of other potential exposure scenarios. Likewise, there exist only few case reports of contact dermatitis, for example eyelid dermatitis, to Fe-oxide pigments in cosmetics.[10,11] In a study on patients with hip arthroplasty, patch testing to different metal preparations also gave positive patch test reactions to Fe. The significance of these findings remained, however, unclear, in view of the study´s small patient number and the absence of controls without implantations.[12] In addition, little is known about the potential number of Fe-sensitized individuals in light of the growing use of pigments and colorants in tattoos and PMU.[13,14] On the other hand, despite being rare, immediate-type reactions to intravenous Fe preparations are well known. Accordingly, studies on the epidemiology, potential pathomechanisms (like the role of carbohydrate shell of intravenously applied Fe in possible complement-activation) and management recommendations were published.[15-17] Over the last two decades, an ever-increasing number of implanted surgical-orthopedic devices/implants is being used, many of which are made of stainless steel containing more than 50% Fe.[18] Thus, in the case of osteosynthesis materials—like plates, wires, screws, or nails—exposure to released Fe can be expected.[19] Particularly, during arthroplasty implantation procedures, Fe-containing abrasion particles are typically introduced at the recipient site through instrument use and wear. In contrast to recent progress made with manufacturing techniques, there remains a knowledge gap regarding most aspects of "internal" metal exposure in implant-bearing patients. Based on data from our outpatient clinic dedicated to allergy diagnostics in patients with suspected metal implant intolerance, orthopaedic-surgical implants in particular, we intended to gain further knowledge regarding potential contact sensitization to Fe in these patients. We aimed to assess the prevalence, but also the epidemiology of Fe sensitization, in particular: (1) exposure conditions (presence of Fe-containing implant, potential tattoo, previous occupational or medical exposure history), (2) type of symptoms/complications, (3) cross-reactivity/co-sensitization to other metals, and (4) evaluation of comparative patch test results of controls without metal implants. In the present study, we report on the prevalence of Fe sensitization, emphasizing the characteristics of Fe-sensitized individuals discovered by our investigation.

2 | METHODS

To better evaluate the Fe contact sensitization, results of three components of our standardized allergological patient workup were analyzed: questionnaire-aided history, information on implant type, and patch testing with an additional late reading on day (D)6. To compare implant bearers with potential controls, we also included patients without metal implantations. The latter presented to our clinic for pre-implant evaluation of suspected metal allergy.

The investigation was approved by the local ethics committee.

2.1 | Patients

From October 15, 2019 (first implementation of the novel extended, Fe-test preparation containing metal test series) until May 31, 2021, a consecutive series of 183 patients (48 male, 135 female; mean age ±SD 62.7 ±11.5) undergoing allergological workup were included in the evaluation. Forty-one patients were examined prior to implantation because of suspected metal allergy, and 142 had metal implants with complications and were suspected of having metal implant allergy. Patients with implant-related complaints had been sent by various referring physicians, mostly orthopaedic surgeons, after a clinical and instrumental examination to exclude symptom elicitors like mechanical problems or infection. A certain selection bias may not be entirely excluded because symptomatic patients with self-reported suspected metal allergy may have been more likely to consult our clinic.

2.2 | Questionnaire-aided history

The questionnaire-aided history included information about smoking, medication, pre-existing diseases, presence of any metallic implants (including dental implants, and evidenced by implant passes), implant-related complaints, history of metal allergy (eg, dermatitis to jewellery, buttons, wrist watches, or other metal objects), and "intolerance/potential allergic reactions" including history of atopic diseases such as allergic rhinitis, atopic eczema, or allergic asthma. A supplemental set of questions was additionally included in case of a positive patch test reaction to Fe. These further questions encompassed leisure- or work-related contact with cement or metal (especially stainless steel) materials, itching/dermatitis upon contact with stainless steel devices, presence of tattoos, and any history of systemic exposure to Fe by infusions or oral (tablet) intake. Furthermore, the orthopaedic WOMAC-questionnaire (Western Ontario and McMaster Universities Arthritis Index) was used to quantify the respective patient´s self-reported view of the artificial joint performance, including items covering pain, stiffness, and functional limitations.

Finally, in addition to patch testing, the German "IVDK/DKG-Background-Questionnaire" (German Information Network of Departments of Dermatology/Contact Dermatitis Research Group) was filled out, so that additional information was available (eg, the presence of tattoos, and any related complications) for the total group of tested patients.

2.3 | Patch testing

All patients underwent testing (1) with the German standard series (DKG 1) as defined by the German Contact Dermatitis Research Group ("DKG") including nickel (Ni; nickel(II)sulfate, 5.0% pet.), cobalt (Co; cobalt(II)chloride, 1.0% pet.), and chromium (Cr; potassium dichromate; 0.5% pet.) preparations and b) with an additional metal series (consisting of titanium (IV)-oxide, 0.1% pet.; molybdenum (V)-chloride, 0.5% pet.; Vanadium-pentoxide, 10.0% pet.; zirconium (IV)-oxide, 0.1% pet; Fe(II)-sulfate, 5.0% pet.; and aluminium(III)-chloride hexahydrate*, 2.0% pet.). The Fe test preparation Fe(II)-sulfate—officially approved for use by the DKG—was taken from the "tattoo colorants series" (DKG 47; formerly "M-Block tattoo-colorants"). For dental implant patients we additionally tested dental metals (DKG 17) and dental technician series (DKG 39). In case of a cemented arthroplasty, a bone cement components series (DKG 48) was also applied, as described earlier.[20,21] Testing was carried out according to the German Contact Dermatitis Research Group (DKG) guidelines.[22] For testing, we used Finn chambers on Scanpor tape, and test preparations provided by Smart Practice (Barsbüttel, Germany), except for the aluminium(III)-chloride hexahydrate preparation, which was purchased from Chemotechnique Diagnostics (Vellinge, Sweden). The substances were applied on the upper back on D0 (day 0). Readings were performed by physicians of the allergy unit on days D2, D3, and—beyond such routine steps—an additional late reading was also done on D6. Reactions classified as +, ++, or +++ were considered as positive.

2.4 | Association analysis and characteristics of Fe-reactive patients

The following was evaluated: (1) to which extent Ni, Co, or Cr reactions were inter-related or associated with self-reported metal allergy in the two groups, and (2) whether Fe patch test reactivity was paralleled by reactions to other metals—in particular to Ni, Cr, or Co. To identify the patient characteristics potentially associated with Fe sensitization, patient history was also taken into account, including atopy status, cutaneous metal intolerance, presence of tattoos, type of implant, and work- or medical therapy–related Fe exposure.

2.5 | Statistics

Data were recorded and analyzed with use of SPSS software (Version 23, IBM, Ehningen, Germany). Potential associations between categorical

TABLE 1 Patient demographics and characteristics

		Pre-implant (n = 41)		Implant patients with complication (n = 142)	
Sex	(m/f)	(4 m, 37 f)		(44 m, 98 f)	
Mean age, y		62.22 ± 11.65		63.01 ± 11.44	
Type of implant	TKR	0	0 %	73	50.8 %
	THR	0	0 %	13	9.3 %
	Joint Resurfacing	0	0 %	11	7.8 %
	Osteosynthesis	0	0 %	19	13.5 %
	Dental	0	0 %	14	10.0 %
	Other[a]	0	0 %	12	8.6 %
Implant-related complaints[b]	Pain	0	0 %	94	66.2 %
	Swelling	0	0 %	79	48.6 %
	Redness	0	0 %	25	17.6 %
	Eczema	0	0 %	14	9.9 %
	Effusion	0	0 %	27	19.0 %
	Reduced range of motion	0	0 %	85	59.9 %
	Other complaints	0	0 %	13	9.2 %
History of atopy[b]	Yes	10 (9AR, 5AA, 5 AE)	24.4 %	36 (28AR, 11AA, 12 AE)	25.4 %
	No	26	63.4 %	101	71.1 %
	Unknown	5	12.2 %	5	3.5 %
Cutaneous metal allergy-related history	Yes	22	53.7 %	55	38.7 %
	No	19	46.3 %	87	61.3 %

Abbreviations: AA, allergic asthma; AE, atopic eczema; AR, allergic rhinoconjunctivitis; f, female; m = male; TKR, total knee replacement; THR, total hip replacement.

[a]For example, stent, pacemaker, shoulder arthroplasty.

[b]Partly more than one complaint/atopic disease per patient.

variables were assessed using the Pearson chi-square test. The observed frequencies were compared with theoretically expected frequencies. An error probability of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient demographics and characteristics

In Table 1, the characteristics of the entire study cohort—41 pre-implant patients and 142 patients with complicated implants—are displayed, including type of implant, metal allergy-related history, history of atopic diseases, and complaints. History of atopy was similar in both groups (24% and 25%, respectively). History suggesting a metal contact allergy (eg, pruritus or eczema upon contact with buttons, wrist watches, jewelry, or other metal items) was reported by 77 of 183 patients (39% of patients with implant complications and 54% of pre-implant patients). The latter percentage was below 100% because some of the pre-implant patients had undergone actual testing—despite a "negative history"—due to previous contradictory "positive" metal patch testing. Most, that is, 73 of the 142 implant bearers, had a total knee replacement (TKR, 51%). The most frequent complaint was pain (66%), followed by swelling (49%). Local implant-associated eczema was present in 10%. Patients often reported multiple complaints.

3.2 | Patch test reactions

The results regarding patch tests with Ni, Co, Cr, and the additional (Fe containing) metal series are summarized in Table 2. The number of patients reacting to any metal was similar, that is, 19 of 41 (46%) in the pre-implant group and 62 of 142 (44%) in the implant-bearing group. Among individuals without self-reported metal allergy, metal reactions were equally distributed: 5/14 (36%) versus 30/86 (35%). The specific reactivity frequencies in the pre-implant patients, the implant bearers and the overall group of 183 patients were: for Ni 39%, 30%, 32%; for Co 17%, 15%, 15%; for Cr 7%, 13%, 11%. Thus, regarding Cr-sensitization, a difference between the pre-implant and implant group was apparent (3/41 vs 18/142), which was most remarkable in those individuals without self-

TABLE 2 Number of positive patch tests for each metal in the patients without implants ("pre-implant") and the implant-bearing patients with complaints

	Pre-implant (n = 41)		Implant patients with complication (n = 142)	
	n	[%]	n	[%]
Metals				
Nickel (II)-sulfate 6(H_2O)	16/41	39.0	42/142	29.6
Cobalt (II)-chloride 6(H_2O)	7/41	17.1	21/142	14.8
Potassium dichromate	3/41	7.3	18/142	12.7
Titanium (IV)-oxide[a]	0/41	0	1/142	0.7
Molybdenum (V)-chloride[a]	0/41	0	1/142	0.7
Vanadium-pentoxide[a]	0/41	0	3/142	2.1
Zirconium (IV)-oxide[a]	0/41	0	0/142	0
Iron (II)-sulfate[a]	2/41	4.9	8/142	5.6
Aluminium (III)-chloride 6(H_2O)[a]	1/41	2.4	1/142	0.7

[a]Test preparations of the additional metal test panel.

TABLE 3 Co-sensitization to other metals in the patients with a positive Fe, Co, or Cr patch test reaction

	Iron (II)-sulfate (n = 10)	Cobalt (II)-chloride 6(H2O) (n = 28)	Potassium dichromate (n = 21)
Iron (II)-sulfate	10/10	2/28	4/21
Nickel (II)-sulfate 6(H_2O)	4/10	19/28	12/21
Cobalt (II)-chloride 6(H_2O)	2/10	28/28	11/21
Potassium dichromate	2/10	11/28	21/21
Titanium (IV)-oxide	0/10	1/28	1/21
Molybdenum (V)-chloride	0/10	1/28	1/21
Vanadium-pentoxide	1/10	2/28	1/21
Zirconium (IV)-oxide	0/10	0/28	0/21
Aluminium (III)-chloride 6(H_2O)	0/10	2/28	2/21

TABLE 4 Characteristics of the 10 Fe-sensitized patients

Patient no.	Age	Sex	Implant type	Atopy	Metal allergy history	Additional metal PT reactions	Presence of tattoo	Occupational or medical metal contact
3399/19	77	f	TKR	No	Yes[a]	Ni, Co, Cr	No	Oral iron supplementation
3427/20	63	f	Pre-implant	No	No	No	No	Occupational metal contact (worker in glass manufacturing company), oral iron supplemention
3440/20	61	f	TKR	No	No	Ni, Co, V	No	Systemic (parenteral) iron supplementation
3451/20	66	f	Pre-implant	No	Yes[b]	Ni	No	Oral iron supplementation
3525/20	55	f	TKR	No	No	Ni, Cr	No	Occupational metal contact (farmer)
3536/21	54	f	TKR	No	No	No	Yes#	Occupational metal contact (camera operator), systemic (parenteral) iron supplementation
3559/21	77	m	Shoulder-arthroplasty	No	No	No	No	Occupational metal contact (metal worker)
3567/21	68	f	TKR	Yes (AR, AE)	No	No	No	Occupational metal contact (work in bus service station), oral iron supplementation
3568/21	56	m	TKR	No	No	No	No	Occupational metal contact (mechanic)
3576/21	66	m	TKR	Yes (AR)	No	No	No	Occupational metal contact (tiler)

Abbreviations: See previous tables; #, asymptomatic; PT, patch test; V, vanadium.
[a]Itching and eczema to metallic wrist watch and watch strap.
[b]Itching and eczema to silver-made necklace.

reported metal allergy (3/22 vs 13/55; $P = .079$). Furthermore—with the limitation of a different group size— reactions to the metals titanium, molybdenum, and vanadium were found only in the implant patients.

Within the additional metal test panel most reactions were observed in response to Fe. Ten of 183 patients (5.5%) had reacted to Fe(II)sulfate, with 6 patients being sensitized exclusively to Fe. Fe-reactors were found both among the patients without implants (2/41) and the implant patients (8/142). Eight of 10 Fe-reactors were detected only at the late reading, that is, on D6. Thus, 80% of Fe-positive individuals would have been missed if only the routine D2/D3 assessment had been done.

3.3 | Association analysis and further characteristics of the Fe-sensitized patients

We found the following associations between metal sensitivities: 12 of 58 Ni-reactive individuals were also Cr-reactive ($P = .1$); 19 of 58 Ni-reactive individuals were also Co-reactive ($P < .001$); and 11 of 21 Cr-reactive patients were also Co-reactive ($P < .001$). These findings are listed in Table 3. Furthermore, 8 of 11 Co- and Cr-reactive patients had a TKR ($P = .037$).

Because Fe-positive reactions were found in 10 patients, we further reviewed their characteristics. First, as mentioned above, most of the reactions were detected onlyl upon late readings, that is, 8 of 10 on D6. Reactors were similarly frequent in pre-implant individuals (2/41; 5%) and implant bearers (8/142; 6%). However, the highest Fe reactivity was observed in patients with complicated knee arthroplasty (7 of 73; 10%). Further peculiarities of the Fe reactors included isolated Fe sensitization (6/10), co-sensitization to Ni (4/10), a history of occupational metal exposure (7/10), and previous (par) enteral Fe therapy (6/10). On the other hand, a history of cutaneous metal intolerance (2/10) or atopy (2/10) was not more frequent than in the overall patient group. Only 1 of 10 had a—asymptomatic—tattoo. The characteristics of the 10 Fe-positive patients are summarized in Table 4.

4 | DISCUSSION

In view of the scarcity of published data, we investigated the prevalence of Fe contact sensitization in a larger patient cohort and sought to identify potential characteristics of Fe-reactive individuals. To our knowledge, this is the first study that addresses this question both in individuals without implantations and implant bearers with complications. Even if individuals with a self-reported suspicion of metal allergy may be overrepresented in the study population, patch testing revealed several peculiarities: (1) different metal sensitization patterns in the two groups; Ni-sensitization was more frequent (39% vs 30%) in the pre-implant patients (paralleled by a higher frequency of self-reported suspicion of metal allergy) and, conversely, Cr-sensitization was lower (7% vs 13%); (2) more than half of Cr-reactive patients were also Co-reactive, and Cr-reactivity was highest (13/55) in symptomatic implant wearers without self-reported metal allergy; (3) most importantly, there was a considerable proportion, that is, 10 of 183 patients (5.5%), with a positive patch test to Fe; (4) in addition, the majority of positive reactions to Fe were detected only on D6 (8/10; 80%).

Previous investigations have shown that positive patch test reactions to Ni, Cr, or Co commonly occur together[23]. Hegewald et al., for example, further described that gender and age impacted the risk to have a positive reaction to Ni and Co (ie, more positive reactions occur in women and at a younger age), whereas older age and construction work influences Co-Cr co-sensitization.[24] Ruff et al. identified 45 Cr reactors in the 1187 patients studied, and 6 of 45 displayed a Co-Cr co-reaction.[25] Both publications, as well as the review by Thyssen and Menné, point to Cr sensitization in occupational settings; nevertheless, the consumer setting is also described and Cr/Co co-sensitization might not have such a strong association with construction workers after all.[26] In our investigation, we detected a high number of CoCr co-sensitizations (11/21), with 8 of 11 (ie, 72%) being found in symptomatic –TKR implant patients. We are not aware of comparable observations previously published. The detection of a relatively higher number of Cr sensitizations in symptomatic arthroplasty bearers has been reported previously.[27-29] However, we cannot compare our findings of four Fe-Ni co-sensitized, and six exclusively Fe-sensitized individuals, with (currently missing) co-sensitization data in the literature. Nevertheless, factors potentially related to Fe sensitization could exist.

When searching for reported occupational type IV sensitization and allergic contact dermatitis to Fe, we retrieved only few publications,[6-8] as well as only few case reports on patients with contact dermatitis from Fe pigmentcontaining cosmetics.[10,11] With regard to the test preparations, in 1986, Van Loon et al. already suggested the inclusion of Fe in an "adequate patch test battery for metal allergy in dentistry," as they had found two reactors to "ferrous citratum" (5.0% aq.), and one patient reacting to "ferric chloride" (2.0% aq.) among 63 patients.[30] In 1993, Motolese et al. had used red iron oxide (2% pet) for the patch testing of enamellers and decorators in the ceramics industry, and these authors reported that 7 of 190 tested individuals were apparently sensitized to it.[6] In 1996, Santucci and coworkers published their observation of a potential additive, that is, enhancing effect, on Ni patch test reactivity, by mixing Ni sulfate with a Fe (III) solution.[31] Given that cement contains Fe oxide (intended to reduce chromate load), this particular source might well be considered a relevant exposure for construction workers.[32] We found only one published investigation[12] where sensitization to Fe was studied in arthroplasty patients. Four of 43 hip arthroplasty patients (resurfacing and conventional hybrid prosthesis) were found to be Fe sensitized, as compared to our findings of 10 of 183 patients, 7 out of 73 being TKR patients. In their publication, Gustafson et al. also reported other metal allergies in the patients studied, but they did not verify any potentially remarkable co-sensitizations. A comparison with our data is difficult because a different Fe preparation (ferric chloride, 2%) was used for testing, and control patients (without implantations) were not included; nonetheless, the findings of Gustafson et al. do support our observations.

The results of our study also underscore the utility of a late patch test reading, as 8 of 10 Fe-reactive patients were discovered only at the D6 reading. Possibly, Fe is a late-reacting allergen. In fact, the added value of delayed readings, in order to detect positive reactions to "late-reacting allergens," is evidenced by numerous publications[20,33,34]—Fe was, however, not included in any of these.

Seven of 10 Fe reactors had occupational metal contact, which could represent a sensitization scenario. However, 8 of 10 Fe reactors had no history of cutaneous metal allergy. On the other hand, 8 were implant wearers and 4 of 10 Fe reactors had other concomitant metal allergies, with Ni always being present. Thus, when looking for the relevance of Fe reactivity, we wondered if further metal exposure, besides epicutaneous contact, might be deducible from more detailed patient (history) data. With regard to potential "non-epicutaneous "exposure, Fe-containing tattoos might represent a likely source. However, only one patient reported the presence of an otherwise uncomplicated tattoo. We also verified any previous Fe therapy, which 6 of 10 patients affirmed. We, however, did not retrieve any information from the remaining 173 patients in order to make an internal comparison. Presumably, there are patients with a history of Fe therapy among those individuals as well, the more since Fe-deficient anemia is relatively common, and frequently treated with use of (temporary) oral supplementation.[35] According to some authors, it seems that Fe deficiency, and resultant anemia, are associated with the onset of type I allergy, such as allergic rhinocunjunctivitis,[36,37] whereas a corrected Fe status might prevent the formation of a type I allergy. In their review on this issue, Roth-Walter et al.[38] described that: "Fe deficiency affects more T-helper (Th)1 than Th2 immune cells," that is, the "proliferative phase of T cells is dependent on Fe supply" and "Th1-associated cytokines IFN-y and the IL-12/IL18-mediated proliferation was found to be severely affected by iron chelators." Conversely, it might be possible that this is balanced by normal Fe homeostasis. Filatova et al. reported on another aspect, stating that a nutritional intervention with a diet sufficient in ion Fe might reduce enteral Ni absorption, thus potentially resulting in positive effects in Ni-allergic individuals.[39] However, we do not know whether the rather high frequency of Fe supplementation within the Fe-sensitized individuals is of any relevance in this context.

The next potential source of Fe is metal implants, in particular, those with higher wear formation and corrosion—namely, articulating implants. Thus, we wondered if the 10% of Fe sensitization in complicated TKR would be of interest. At first glance, Fe is not—as opposed to osteosynthesis or some total hip replacement (THR) models—a frequent TKR alloy constituent. The most common implant material in TKR is a CoCrMo alloy, which according to the ISO standards for implant materials,[40,41] should have an Fe mass fraction between 0.75% and 1.0% (similar to Ni, which should have a mass fraction below 1.0%). However, there might also be an underestimated source of Fe during a TKR surgery: wear particles generated by the intraoperative instruments. It is well-known that considerable amounts of Fe-containing particles may be created by intraoperative instruments, mainly saw blocks and saw blades, during the preparation of the bony surfaces.[42-44] These two instruments are usually made out of stainless steel, which consists mainly of Fe. Even though it is a standard procedure to irrigate the knee joint several times with saline solution and a pulse lavage system during surgery, a significant

amount of debris can remain in the joints, as demonstrated by a study of De Baets et al.[44] Nevertheless, only 1.5% of the debris collected after surgery were metal particles, accounting for an average of 1.96 mg (range 0 - 7.2 mg). It is tempting to consider this as a potential "exposure scenario" in which particle effects and metal ion exposure might enable transition to delayed-type hypersensitivity.[45]

Despite some weaknesses of the current study, including highly selective patient groups, different group sizes (implant vs non-implant patients), we believe that our findings add to the understanding of Fe as a potentially underestimated metal allergen. Furthermore, these findings might stimulate further research into this topic.

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AUTHOR CONTRIBUTIONS

Eva Oppel: Conceptualization (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Florian Kapp:** Investigation (supporting); methodology (supporting). **Ann-Sophie Bohm:** Investigation (supporting); methodology (supporting). **Ralf Pohl:** Conceptualization (equal); investigation (supporting); methodology (supporting). **Peter Thomas:** Writing – original draft (equal); writing – review and editing (equal). **Burkhard Summer:** Conceptualization (equal); data curation (equal); writing – original draft (equal); writing – review and editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONFLICTS OF INTEREST

None to declare

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