

Influence of Surface Coating on Metal Ion Release: Evaluation in Patients With Metal Allergy

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abstract

Nickel, chromium, and cobalt in stainless steel and Cobalt-chrome-molybdenum (CoCrMo) alloys may induce allergy. The objectives of this study were to evaluate surface coating regarding ion release, patch test reactivity, and arthroplasty performance. Materials and methods included patch test in 31 patients with metal allergy and 30 patients with no allergy to stainless steel and CoCrMo disks that are uncoated or coated by titanium nitride/zirconium nitride (TiN/ZrN). Assessment include atomic absorption spectrometry of released nickel, cobalt, and chromium from the disks after exposure to distilled water, artificial sweat and culture medium. Results showed that both coatings reduced the nickel and chromium release from stainless steel and CoCrMo disks and mostly the cobalt release from the disks (maximally 11.755 $\mu\text{g}/\text{cm}^2/5$ d to 1.624 by Ti-N and to 0.442 by ZrN). Six of the 31 patients with metal allergy reacted to uncoated disks, but none reacted to the coated disks. The current authors report on exemplary patients with metal allergy who had symptom relief by revision with surface-coated arthroplasty. The authors concluded that the surface coating may prevent cutaneous and peri-implant allergic reactions. [*Orthopedics*. 2016; 39(3):S24-S30.]

Metal allergy—specifically contact allergy to cobalt (Co), chromium (Cr) or nickel (Ni)—is frequently found in the general population.¹ The mean sensitization rates may range between 13% (Ni) and 1.1% (Cr), with further differences based on age and sex.² Eczema from metallic daily-use articles typically develops following prolonged or repeated skin contact to items such as jewelry, earrings, and watch bands.

With regard to orthopedic surgical use, stainless steel based osteosynthesis materials and CoCrMo alloys in arthroplasty are mostly evaluated according to fracture healing and biomechanical long-term results.³⁻⁵ However, all implanted metal alloys corrode, and the process of abrasive wear additionally produces particles in joint replacement. Thus Co, Cr, and Ni was detected in peri-implant tissue, blood, and urine, and particle dissemination was

also found in lymph nodes and various organs—particularly in association with joint replacement prostheses.⁶⁻⁸ In the 1960s and 1970s, excessive metal release and particle formation in the early used metal-on-metal (MoM) total hip arthroplasty (THA) was linked to peri-implant foreign body reactions, often resulting in bone resorption and implant loosening.^{9,10} In early THA patients, an elevated rate of

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metal sensitization was also observed.^{11,12} In association with allergy to Co, Cr, or Ni, delayed-type hypersensitivity reactions to implanted metals have been described under the picture of local or generalized eczema, impaired wound, or fracture healing and implant loosening.¹³⁻¹⁶ In the new generation of MoM THA, much smaller particles are generated,¹⁷ and initially the risk for hypersensitivity was considered to be very low.¹⁸ Peri-implant tissue retrieved from aseptically loosened MoM arthroplasties has in part been reported to show characteristics of delayed-type hypersensitivity reactions like lymphocytic infiltrates and pseudo-lymph follicles.¹⁹⁻²² In such selected patients presenting with peri-implant T-lymphocytic inflammation, a high rate of metal allergy was found.²³ Based on previous observations,²⁴ the aim of the present study was to evaluate the potential of cutaneous reactivity to stainless steel and CoCrMo disks and its prevention by surface coating in patients with a proven contact allergy to Ni, Co, or Cr. In addition, patch test reactivity was compared with the amount of released Ni, Co, or Cr in eluates prepared from uncoated and surface-coated metal disks. Finally, symptom course is reported in exemplary metal allergic patients after revision by coated arthroplasty.

MATERIALS AND METHODS

Metal Disks

The metal disks were made of stainless steel and a CoCrMo alloy, both commonly used in orthopedic surgical implants. The metal disks were provided by B. Braun Aesculap, Tuttlingen, Germany. The stainless steel (according to ISO 5832-9) was a more corrosion resistant type due to its nitrogen alloyed manufacturing. Its Cr content was 20.79, its Ni content was 9.81 wt %. The CoCrMo alloy (according to ISO 5832-12) was used as wrought material, having a more homogeneous structure but identical chemical gross composition as the cast type. Its Co content was 65.2, its Cr content was 27.3, and its Ni content

was 0.3 wt %. The chemical composition of the alloy materials used here is in accordance with the requirements of the respective ISO standards. The composition of the test samples was assessed by B. Braun Aesculap by emission spectrometry.

Processing and Surface Coating of the Disks

The disks were further manufactured by B. Braun Aesculap, including machining (turning, slip grinding) to a diameter of 12 mm, thickness of 0.5 mm, and surface roughness of $r_a=0.5\pm0.2\ \mu\text{m}$. Two types of surface coating were applied:

Titanium nitride (TiN) coating. Monolayer ceramic coating of stainless steel and CoCrMo disks was done by physical vapor deposition (PVD), which involves coating the implant during the vapor phase in a high-vacuum chamber to which nitrogen is added.

Zirconium nitride (ZrN) coating. A multilayer coating system consisting of a thin adhesive chrome layer, 5 alternating intermediate layers out of chrome nitride (CrN)-chrome carbonitride (CrCN), and a final shielding zirconium nitride (ZrN) layer was used. Through PVD, this 7-layer coating was applied on the stainless steel and CoCrMo disks. Gradient fashion of the CrN-CrCN layers facilitates bridging the difference in hardness and tension between CoCrMo and the very hard ZrN shielding layer. Thus, mechanical integrity is not lost. The interfaces between the layers act as further diffusion barrier. The final ceramic ZrN layer seals the system and is highly biocompatible.

Its abrasive properties were evaluated in an in vitro simulation according to ISO 14243-1:2002(E) through 5 million cycles with a frequency of 1 Hz and had proven to be much lower in coated vs uncoated CoCrMo-based implants.²⁵

The disks were laser marked for identification, cleaned, packaged according to the typical procedures used for medical devices, and sterilized by γ -irradiation with a dose of about 30 kGy.

Metal Elution

The CoCrMo disks (as is, TiN coated, ZrN coated) and stainless steel disks (as is, TiN coated, ZrN coated) were put into flat bottom polystyrene²⁴ well culture plates (culture plates from Corning Inc, Corning, Kaiserslautern, Germany) and incubated for 5 days in artificial sweat (AS; 0.5% NaCl, 0.1% urea, 0.1% lactic acid, pH 6.5 according to EN 1811), complete culture medium (10% AB-serum containing RPMI 1640 medium supplemented with HEPES 25 mm (Biochrom KG Seromed, Berlin, Germany), L-Glutamine (Biochrom KG Seromed, Berlin, Germany), antibiotic-antimycotic solution (Gibco, Carlsbad, California), nonessential amino acids, and minimum essential medium vitamins (Biochrom KG Seromed, Berlin, Germany), or distilled water (H_2O). The metal disks (uncovered surface: $0.245\ \text{cm}^2$) were exposed to 1 mL elution medium over 5 days at 37°C under sterile conditions. The eluates were obtained in quadruplicate, (ie, in 4 separate experimental series). The eluates were then pooled and the metal content was assessed by a graphite furnace atomic absorption spectrometer.

Atomic Absorption Spectrometry

Determination of Ni, Co, and Cr in the pooled metal disk eluates was performed by graphite furnace atomic absorption spectrometry (AAS) with Zeemann-effect background correction system (SIMAA 6100, THGA Graphite Furnace, autosampler AS 800, Perkin Elmer, Rodgau, Germany) after microwave digestion of the samples. As previously described,²⁴ the results were obtained from a 3-point calibration curve prepared from Ni, Cr, and Co standard solutions (Atomic Absorption Standard Solution, Sigma Chemical Company, St. Louis, Missouri). Four independent measurements of the eluates were taken, and the mean metal content is given as $\mu\text{g}/\text{cm}^2/5\ \text{d}$. For each set of tests, a blank element solution had been included in AAS measurement, and these



Figure 1. Eczematous reaction upon knee arthroplasty in a patient with chromium allergy.



Figure 2. Skin condition after revision and exchange of the implant with multilayer coating.

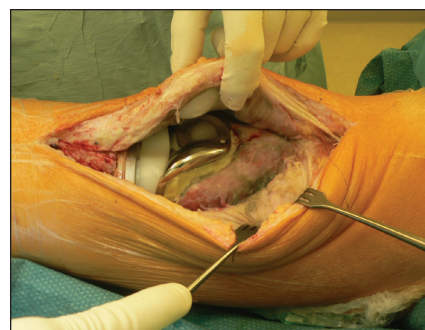


Figure 3. Intraoperative view of the patient with cobalt hypersensitivity. Often seen is the grey synovia due to metal debris.

Table 1

Results of Metal Liberation From Stainless Steel Disks

Eluent	Ni Release From Stainless Steel [$\mu\text{g}/\text{cm}^2/5\text{ d}$]			Co Release From Stainless Steel [$\mu\text{g}/\text{cm}^2/5\text{ d}$]			Cr Release From Stainless Steel [$\mu\text{g}/\text{cm}^2/5\text{ d}$]		
	Uncoated	TiN	ZrN	Uncoated	TiN	ZrN	Uncoated	TiN	ZrN
Cell culture medium	1.464 ± 0.211	0.409 ± 0.042	0.339 ± 0.127	ND	ND	ND	0.649 ± 0.259	0.138 ± 0.006	0.129 ± 0.073
Distilled water	3.278 ± 0.697	1.055 ± 0.025	1.032 ± 0.353	0.042 ± 0.079	ND	0.142 ± 0.263	0.082 ± 0.034	0.031 ± 0.006	0.033 ± 0.022
Artificial sweat	2.351 ± 0.652	0.669 ± 0.018	0.686 ± 0.132	0.018 ± 0.155	ND	ND	1.218 ± 0.172	0.413 ± 0.005	0.413 ± 0.060

Abbreviations: Co, cobalt; Cr, chromium; ND, not detectable; TiN, titanium nitride; ZrN, zirconium nitride.

Release of metal ions from stainless steel disks uncoated and with TiN or ZrN coating by exposure to different elution media (cell culture medium, distilled water, artificial sweat) over 5 days. Metal release was assessed by atomic absorption spectrometry. The basic metal content in the elution media was subtracted. Mean of 4 measurements is given as $\mu\text{g}/\text{cm}^2/5\text{ d}$ ($\pm$ SD).

results were subtracted of the samples. Detection limits were 0.00007 $\mu\text{g}/\text{mL}$ for Ni, 0.00015 $\mu\text{g}/\text{mL}$ for Co, and 0.00035 $\mu\text{g}/\text{mL}$ for Cr.

Patients and Patch Testing

A consecutive series of 31 patients with metal allergy (24 female; 7 male; age 25-74 years, mean 50.35; history positive; patch test reactivity to Ni, Co, or Cr) and 30 non-allergic patients (22 female, 8 male; age 20-88 years, mean 49.28; history and patch test negative) volunteered upon informed consent to getting additionally patch tested to the 6 metal disks (CoCrMo and stainless steel uncoated and with 2 different coatings). This procedure was approved by the local ethics committee. Twenty-three of the

patients with metal allergy were allergic to Ni, 11 were allergic to Co, and 7 were allergic to Cr. Twelve of 31 were allergic to more than 1 metal. The disks were fixed on the patients' backs and, identically to routine patch test, removed after 48 hours. Evaluation of the skin reactions was done upon removal (48-hour application) and at 72 hours. Reactions were classified according to the standard German Contact Dermatitis Research Group criteria.

Exemplary Arthroplasty Patients

Rarely do the current authors see patients with hypersensitivity due to metal implants. The reaction to the implant can be with swelling, pain, and skin reaction, as seen in a female patient starting with

the symptoms shortly after implantation (Figures 1-2). The patch test was positive to chromium, and after changing the implant to a ZrN multilayer coated implant of the same design, the skin wound healed without complications, and the eczema disappeared.

Another patient had several knee revisions before it was realized that he had a cobalt hypersensitivity. He always had pain and a massive swelling of the knee. The correct diagnosis took at least 5 years to be made, and only after changing the implant the third time and then to zirconium surface hardening revision, was the problem solved.

Intraoperatively, the gray synovia was seen (Figure 3).

Table 2

Results of Metal Liberation From CoCrMo Disks

Eluent	Ni Release From CoCrMo Alloy [$\mu\text{g}/\text{cm}^2/5\text{ d}$]			Co Release From CoCrMo Alloy [$\mu\text{g}/\text{cm}^2/5\text{ d}$]			Cr Release From CoCrMo Alloy [$\mu\text{g}/\text{cm}^2/5\text{ d}$]		
	Uncoated	TiN	ZrN	Uncoated	TiN	ZrN	Uncoated	TiN	ZrN
Cell culture medium	0.147 ± 0.161	ND	0.013 ± 0.011	10.296 ± 1.788	1.123 ± 0.060	0.285 ± 0.021	0.594 ± 0.206	0.079 ± 0.077	0.100 ± 0.140
Distilled water	0.131 ± 0.046	0.003 ± 0.041	ND	11.755 ± 2.126	1.624 ± 0.632	0.442 ± 0.230	0.063 ± 0.006	0.001 ± 0.011	0.036 ± 0.072
Artificial sweat	0.117 ± 0.053	ND	ND	9.649 ± 4.466	1.337 ± 0.232	0.399 ± 0.111	0.626 ± 0.064	0.080 ± 0.027	0.041 ± 0.019

Abbreviations: Co, cobalt; CoCrMo, cobalt-chrome-molybdenum; Cr, chromium; ND, not detectable; TiN, titanium nitride; ZrN, zirconium nitride. Release of metal ions from CoCrMo alloy disks uncoated and with TiN or ZrN coating by exposure to different elution media (cell culture medium, distilled water, artificial sweat) over 5 days. Metal release was assessed by atomic absorption spectrometry. The basic metal content in the elution media was subtracted. Mean of 4 measurements is given as $\mu\text{g}/\text{cm}^2/5\text{ d}$ (SD).

RESULTS

Metal Release

Since there were traces of Ni, Co, and Cr already in the eluents (particularly culture medium), this background level was subtracted from the metal disk-derived eluates. The results of metal liberation from stainless steel disks are given in **Table 1**; the respective data for CoCrMo disks are shown in **Table 2**.

Stainless steel disks. There was no Co release upon contact to culture medium and almost none to H_2O and to AS ($0.042\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$ and $0.018\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$, respectively). Correspondingly, no Co release was observed from the coated disks except for ZrN coated stainless steel in H_2O ($0.142\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$). Most Cr release was induced by AS ($1.218\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$) most Ni release by H_2O ($0.697\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$). Both surface coatings reduced this Ni and Cr liberation (**Table 1**).

CoCrMo disks. Only small amounts of Ni and Cr were detected in the different eluents (maximal Ni release by medium: $0.147\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$; maximal Cr release by artificial sweat: $0.626\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$). In contrast, there was a marked Co release upon all eluents (culture medium, $10.296\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$; H_2O , $11.755\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$; AS: $9.649\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$). Ti-N and Zr-N coating reduced the metal release (**Table 2**).

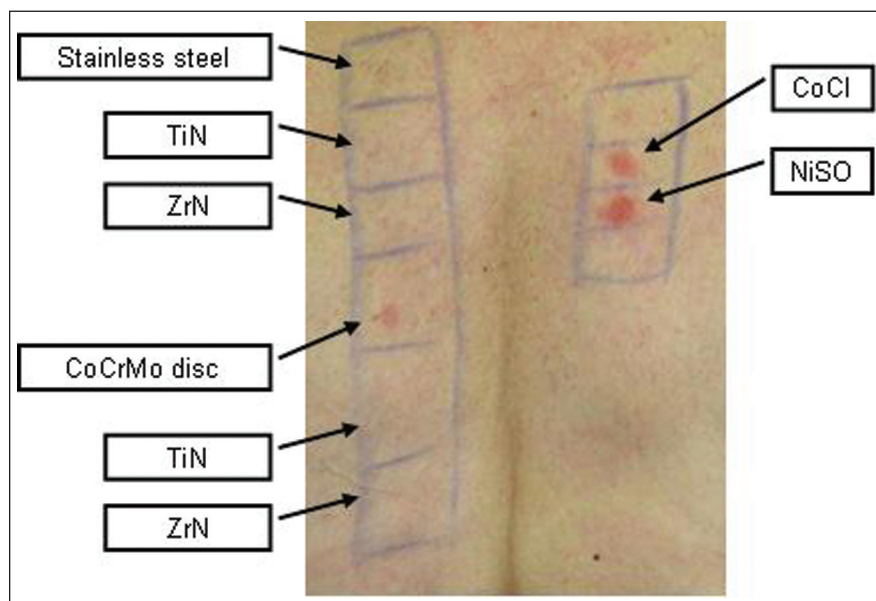


Figure 4. Patch test reactivity to the uncoated and coated disks in a nickel and cobalt allergic individual.

Reduction was for example for Co in the H_2O -eluate from $11.755\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$ to $1.624\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$ by TiN coating and to $0.442\text{ }\mu\text{g}/\text{cm}^2/5\text{ d}$ by ZrN coating.

Patch Testing

A total of 5 patients with metal allergy reacted to the uncoated metal disks (1/5 to both variants). Two of the 31 patients with metal allergy—of whom 23 were allergic to Ni—showed contact allergic reaction to the stainless steel disk. Four of

the patients with metal allergy reacted to the CoCrMo-alloy disk. All of these 4 reactors had a concomitant allergic reaction to the Co standard patch test, 3 were additionally allergic to Cr, and 3 to Ni. The reaction to the disk was + in 3 individuals; 1 person gave a ++ reaction to it. Thus, 4 of the 11 patients allergic to Co (36%) within the 31 patients with metal allergy had reacted to the CoCrMo alloy disk (**Figure 4**). The patch test results of the 31 patients with metal allergy are given

Table 3

Patch Test Reactions in the 31 Patients With Metal Allergy

Contact Allergen	Patients Reacting (n)	%
Nickel(II)-sulfate	23	74.2
Cobalt(II)-chloride	11	35.5
Potassium-dichromate	7	22.6
Balsam of Peru	2	6.5
Compositae Mix	2	6.5
Fragrance-Mix	1	3.2
Dibromocyanobutane, Phenoxyethanol	1	3.2
Propolis	1	3.2
Colophonium	0	0
Lanolin	0	0
Phenylendiamine	0	0
Formaldehyde	0	0
Lyrar	0	0
Thiuram-Mix	0	0
Mercapto-Mix	0	0
Epoxide resin	0	0
p-tert-Butylphenol-Formaldehyde resin	0	0
Turpentine	0	0
(Chlor)-Methylisothiazolinone	0	0
Paraben-Mix	0	0
Cetylstearyl-alcohol	0	0
Zink-diethyldithiocarbamate	0	0
Bufexamac	0	0
Mercaptobenzothiazole	0	0
Fragrance-Mix II	0	0
Bronopol	0	0
Stainless steel uncoated	2	6.5
Stainless steel TiN coated	0	0
Stainless steel ZrN coated	0	0
CoCrMo alloy uncoated	4	12.9
CoCrMo alloy TiN coated	0	0
CoCrMo alloy ZrN coated	0	0

Abbreviations: CoCrMo; cobalt-chrome-molybdenum; TiN, titanium nitride; ZrN, zirconium nitride.

in **Table 3**. None of these patients had reacted to the coated disks. The 30 non-allergic individuals had not reacted to any of the disks.

DISCUSSION

The implantation of stainless steel and CoCrMo-based biomedical devices

is increasing, particularly in osteosynthesis and joint replacement. Upon corrosion and wear formation, metal ions are released from such materials in surrounding tissues. An increasing number of observations points to metal-induced potential toxic²⁶ or hyperergic reactions^{24,27} leading to persisting symptoms

or even implant failure. The current authors thus examined in a patch test model if a) this release of the different metals from CoCrMo disk or stainless steel disk was sufficient to elicit an allergic skin test reaction in patients with a positive patch test to Ni, Cr, or Co; b) a link could be found between the results of skin testing, and the release rates of respective metals as assessed by AAS of eluates from the metal disks; c) whether a surface coating of such metal disks could prevent metal ion release and subsequent elicitation of allergic skin reaction. Patch testing to the stainless steel disk (in the current authors' case, a nitrogen alloyed stainless steel according to ISO 5832-9) gave only 2 positive, allergic reactions in the 31 metal-allergic individuals tested, of whom 23 were allergic to Ni. Correspondingly, a low release of Ni (maximally 3.278 µg/cm²/5 d upon exposure to distilled water) was seen in the elution experiments. These patch test results are in accordance with a previous investigation, showing patch test reactivity to a stainless steel material only in 2 out of 66 individuals.²⁶ Upon the use of TiN and ZrN coated stainless disks, none of the patients with metal allergy reacted to it, and Ni release was found to markedly be reduced. With regard to the CoCrMo disks, they mainly consist of Co. Thus, it is reasonable that all of the 4 reactors to them were allergic to Co. In the elution experiments, CoCrMo disks showed a predominant Co release, but also some Cr and Ni liberation. TiN or ZrN coatings had both prevented the skin reactivity and reduced the metal liberation. Taken together, these findings indicate—in accordance with other investigations^{24,28,29}—that the concentration of released metals is high enough to elicit allergic patch test reactions in patients allergic to Ni, Co, or Cr, and secondly that surface coating is preventing such reactions by reducing the metal release.

It is a well known observation, that elevated levels of Ni, Co, and Cr can be found in patients with arthroplasty,

particularly the MoM type. It was also reported, that the presence of proteins increase the corrosion of stainless steel and of pure metals.³⁰ The current authors observed a similar effect upon use of AB-serum containing medium as eluent. The amount of Ni release from stainless steel may also depend on manufacturing aspects. Haudrechy et al reported that non-resulfurized stainless steels with a low sulfur content did not elicit patch test reactions, whereas patch test reactivity was seen in 14% of the patients to a high sulfur stainless AISI 303 steel and even in 96% to nickel-plated samples.³¹ In vivo, metal release from implanted devices may be enhanced by low pH, concomitant infection, and the presence of proteins^{30,32}—and in articulating surfaces also by wear formation.

Since metals are frequent elicitors of contact allergy in the general population, potential threshold levels for elicitation of cutaneous contact allergy have been investigated by evaluation of metal release from and patch test reactivity to Ni-containing disks^{29,33} and chromated disks.³⁴ The heterogenous experimental settings in the various studies led, however, to only partly comparable results. The respective threshold levels were reported for Ni as 1 µg/cm²/week and for Cr as 0.3 µg/cm²/week after a short 20-minute elution. In the case of Co, serial dilutions of CoCl₂ in distilled H₂O were used for patch test in 9 patients allergic to Co and the minimal delayed-type hypersensitivity eliciting concentration was reported as 2.26 ng/mL.³⁵ Data regarding CoCrMo-based materials are still incomplete. There surely exist strongly sensitized individuals in whom minute exposure to metals may already provoke skin eruptions.³⁶ In general, however, as alloys with a Ni release >1 µg/cm²/week were found to produce strong eczematous, allergic reactions in Ni-sensitive individuals,²⁹ it was suggested to use alloys with a Ni release rate of less than 0.5 µg/cm²/week for metal items designed

for prolonged skin contact. This recommendation was enforced by the “Nickel Directive” of the European Parliament.

The diagnosis of metal implant allergy still remains a diagnosis of exclusion and relies on patch test, histology, and lymphocyte transformation test.³⁷ However, alternative knee arthroplasty materials are available for patients with metal allergy and are already applied.³⁸ An exemplary patient with metal allergy was presented by Thomsen et al having symptom relief after revision with identical knee arthroplasty model. The only modification was surface coating to prevent metal ion release.³⁹ In a study surveying a large number of surgeons on what they prefer and how often they see this problem, most surgeons responded in a different manner. Multilayer coating or surface hardening was the most common recommendation before single layer coating or the standard implant.⁴⁰

In summary, to date elicitation thresholds for cutaneous metal allergic reactions have been studied mostly for Ni contact allergy. Respective recommendations do not exist for Co-containing materials. Furthermore, potential allergy elicitation thresholds in peri-implant tissue are not known. However, the results of the present study show that also Co release from CoCrMo alloys is sufficient to elicit a positive cutaneous reaction. Furthermore, surface coating could prevent, in the experimental model presented here, allergic cutaneous reactions to alloy disks in patients with metal allergy. Such coating also offers a promising approach to reduce peri-implant metal-related hyperreactivity reactions. Follow-up studies in respective patients with metal allergy who are receiving surface coated arthroplasty are being presently undertaken.

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