Authors and Disclosures

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From Dermatitis

Cutaneous and Systemic Hypersensitivity Reactions to Metallic Implants

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Abstract and Introduction

Abstract

Cutaneous reactions to metal implants, orthopedic or otherwise, are well documented in the literature. The first case of a dermatitis reaction over a stainless steel fracture plate was described in 1966. Most skin reactions are eczematous and allergic in nature, although urticarial, bullous, and vasculitic eruptions may occur. Also, more complex immune reactions may develop around the implants, resulting in pain, inflammation, and loosening. Nickel, cobalt, and chromium are the three most common metals that elicit both cutaneous and extracutaneous allergic reactions from chronic internal exposure. However, other metal ions as well as bone cement components can cause such hypersensitivity reactions. To complicate things, patients may also develop delayed-type hypersensitivity reactions to metals (ie, in-stent restenosis, prosthesis loosening, inflammation, pain, or allergic contact dermatitis) following the insertion of intravascular stents, dental implants, cardiac pacemakers, or implanted gynecologic devices. Despite repeated attempts by researchers and clinicians to further understand this difficult area of medicine, the association between metal sensitivity and cutaneous allergic reactions remains to be fully understood. This review provides an update of the current knowledge in this field and should be valuable to health care providers who manage patients with conditions related to this field.

Introduction

Contact Allergy to metals such as nickel, cobalt, and chromium is prevalent in the general population. It is estimated that up to 17% of women and 3% of men are nickel allergic, and that about 1 to 2% are allergic to cobalt, chromium, or both.[1] Metal allergy is mainly caused by prolonged or repeated skin exposure to consumer items such as jewelry, cell phones,[2] clothing fasteners,[3] and leather goods.[4] In some countries, a significant proportion of metal allergy derives from occupational exposure in the metal and construction industries.[5] Independent of the primary cause of metal sensitization, the insertion of metallic implants may result in eczematous eruptions on the skin overlying the implant or in device failure caused by delayed-type hypersensitivity (DTH) (eg, chronic inflammation, pain, loosening of joint prostheses, or restenosis of cardiac stents). In an aging population, the putative association between metal allergy and device failure due to DTH may be a problem of growing significance.[6] This review aims to update the reader on the general aspects of this complex topic and to briefly discuss future challenges.

Compositions of Metal Implants

Most orthopedic dental implants, intracoronary stents, prosthetic valves, endovascular prostheses and some gynecologic devices are made from metal alloys (Table 1). Orthopedic implants are most often made from steel (stainless or cobalt-chromium alloys), vitallium, or titanium.[7–10] A newer metal, oxidized zirconium (Oxinium, Smith & Nephew, San Antonio, TX), is also available and is primarily used in knee prostheses. Metals used in metallic dental implants include mercury amalgam (an alloy of mercury with tin, silver, zinc, or copper), gold alloys, chromium-based alloys, stainless steel, palladium, titanium, and cobalt alloys.[11] Endovascular devices (metal stents, abdominal aortic aneurysm endografts, and patent foramen ovale occluders) are frequently manufactured from metal alloys such as stainless steel and nitinol.[12] Cardiac pacemakers are often made of titanium; hence, titanium is the most common allergen to elicit pacemaker-induced dermatitis.[13] As expected, metal ions are the most frequent causative allergens in allergic cutaneous dermatitis

associated with all the aforementioned devices. The components of these materials are summarized in Table 2.[8,10,14,15]

Table 1. Some Metals and Metal Alloys Used in Implants

Implant Type	Stainless Steel	Metal Alloy							Copper
		Co-Cr-Mo	Vitallium	Titanium	Mercury	Cr-Co-Ni	Gold	Nitinol	
Orthopedic	+	+	+	+	—	—	—	—	—
Dental	+	—	—	+	+	+	+	—	—
Endovascular	+	—	—	+	—	+	+	+	—
Cardiac pacemaker	—	—	—	+	—	+	—	+	—
Gynecologic	+	—	—	+	—	—	—	+	+

Co = cobalt; Cr = chromium; Mo = molybdenum; Ni = nickel.

Table 2. Components of Selected Alloys Used in Metal Implants

Implant Alloy	Metal	Approximate %
316L stainless steel[14]	Nickel	8.3–35
	Chromium	20
	Manganese	2
	Molybdenum	2–3
	Nitrogen	0.1
	Carbon	0.03
	Sulfur	0.03
	Silicon	0.75
	Phosphorus	0.045
	Iron	Balance
Cobalt-chromiummolybdenum steel (ASTM F75)[15]	Chromium	27–30
	Molybdenum	5–7
	Nickel	< 0.5
	Iron	< 0.75
	Carbon	< 0.35
	Silicone	< 1
	Manganese	< 1
	Tungsten	< 0.2
	Phosphorus	< 0.02
	Sulfur	< 0.01
	Nitrogen	< 0.25
	Aluminum	< 0.1
	Titanium	< 0.1
	Boron	< 0.01
	Cobalt	Balance

Vitallium[8]	Cobalt	61
	Chromium	32
	Silicon	0.5
	Manganese	0.5
	Carbon	0.02
	Boron	0.1
	Molybdenum	5.6
	Iron	None
Titanium	Titanium	89.9
	Aluminum	5.5–6.5
	Vanadium	3.5–4.5
	Nickel[10]	Trace
Nitinol	Titanium	55
	Nickel	45
Oxinium	Zirconium (oxidized)	97.5
	Niobium	2.5
	Nickel	None

ASTM = American Society for Testing and Materials.

DTH Reactions

In nonsensitized subjects, de novo metal sensitization may result from a hypersensitivity response to metal ions after either corrosion or mechanical wear of an implant.[9,16] When metals come into contact with biologic fluids, they undergo corrosion to release ionic compounds, which may then bind to endogenous proteins to form metal-protein complexes. Other activation mechanisms have been described in regard to nickel (eg, nickel may directly activate the T-cell receptor in a way that is reminiscent of superantigens).[17] It has been shown that metal ions are liberated from cobalt-chromium-molybdenum alloys that are not subjected to mechanical wear and that these metal ions accumulate in rat liver and kidney tissue.[18] Independent of the mechanism that results in metal ion release and exposure, metal ion exposure may result in activation of macrophages and a DTH response.

Implant-related Allergic Contact Dermatitis

The most common types of cutaneous allergic reactions associated with metallic implants are eczematous in nature, although urticaria and vasculitis have occasionally been reported.[7,9] Eruptions may be localized or generalized or both. Localized eruptions present as dermatitis primarily affecting the skin overlying the site of the implant. Generalized eruptions most often present as eczematous reactions and occur equally in association with static and dynamic implants. Various diagnostic criteria have been proposed for implant-induced cutaneous allergic reactions. The most recent criteria were proposed in 1992 and are included in Table 3.[19] We are currently developing an updated approach.

Table 3. Diagnostic Criteria for Metal-Induced Cutaneous Allergic Reactions

1. Chronic eczema beginning weeks or months after the implant
2. Eczema most severe around the implant site
3. Absence of other contact allergens or systemic cause
4. Patch tests positive or strongly positive for one of the metals in the alloy
5. Complete and rapid recovery after total removal of foreign metal implant

Adapted from Merle C et al.[19]

The few prospective longitudinal studies that have examined the association between metal sensitivity and cutaneous allergic reactions are summarized in Table 4. The first study was performed by Carlsson and Möller in 1989.[20] A series of 18 patients were identified as metal allergic prior to receiving stainless steel orthopedic implants. None of the 18 patients who were observed for up to 6 years had complications despite confirmed allergy to one of the metals in his or her device. Later studies suggest that up to 5% of all patients with orthopedic implants and up to 21% of patients with preoperative metal sensitivity may develop cutaneous allergic reactions upon reexposure to the same metal.[21] More longitudinal prospective studies are needed to better define the actual prevalence of implant-induced reactions and determine whether metal-allergic subjects have an increased risk of complications. In Germany, national databases are currently being created to better study the association between metal allergy and implant failure.[22]

Table 4. Prospective Longitudinal Studies and Reviews*

Study or Review	Reference No.	Total Patients	Conclusions
Carlsson and Möller, 1989	20	18	Metal allergic patients, screened before receiving stainless steel orthopedic implants. None had issues despite confirmed allergy to one of the metals in their device (6-year follow-up).
Gawkrodger, 1993	7	N/A	"…it appears that most patients who are metal-sensitive can safely receive an orthopedic implant containing that metal without the risk of cutaneous or systemic complications."
Merritt and Rodrigo, 1996	115	22	< 1% develop cutaneous reactions versus 20–25% of patients who develop implant-induced metal sensitivity without any allergic skin manifestations
Hallab et al, 2001	9	N/A	Metals corrode in biologic systems, allowing for hapten formation. These degradation products of the implant may cause increased metal hypersensitivity and implant failure. Those with failed implants have a higher rate of dermal sensitivity.
Niki et al, 2006	21	92	26% of screened patients (*n* = 92) had positive lymphocyte stimulation tests to at least one metal (Ni, Co, Cr, Fe). In those with metal positives prior to implantation, 21% (5/24) developed cutaneous dermatitis at the site of implantation and (in some cases) widespread dermatitis; 5% of the total study group with metal orthopedic implants developed cutaneous allergic reactions.
Thyssen et al, 2009	41	356	The risk of surgical revision was not increased in patients with metal allergies, and the risk of metal allergy was not increased in patients who were operated on, in comparison with controls.
Eben et al, 2010	117	92	66/92 had symptoms (pain, reduced motion, swelling).
			Rates of allergy: nickel, patients (24.2%); cobalt, 6.1%; chromium, 3.0
			Symptomatic patients (31.8%) showed an allergic reaction to bone cement components (gentamicin 23.8%, benzoyl peroxide 10.6%, hydroquinone 4.5%)
			Sensitization rates in symptom-free patients: 3.8% for nickel, cobalt, chromium; 15.4% for gentamicin

Fe = iron; Co = cobalt; Cr = chromium; N/A = not applicable; Ni = nickel.
*List may not be exhaustive.

Allergic Contact Dermatitis and Extracutaneous Complications from Orthopedic Implants

The first case of metal-related dermatitis was reported in 1966;[23] since then, a growing number of reports of such cases have been published in the literature.[8,17,21,24–28] By 1986, 42 such cases had been documented; 30 patients developed dermatitis in the setting of a static implant, whereas the remaining 12 patients with dermatitis had received a dynamic joint prosthesis.[24] The condition of 18 (42.9%) of the 42 patients was diagnosed as "eczematous dermatitis." Generalized eruptions in the form of erythema, [29] urticaria,[30] and vasculitis were also reported.[19,31] An example of dermatitis adjacent to a static titanium implant is shown in Figure 1.

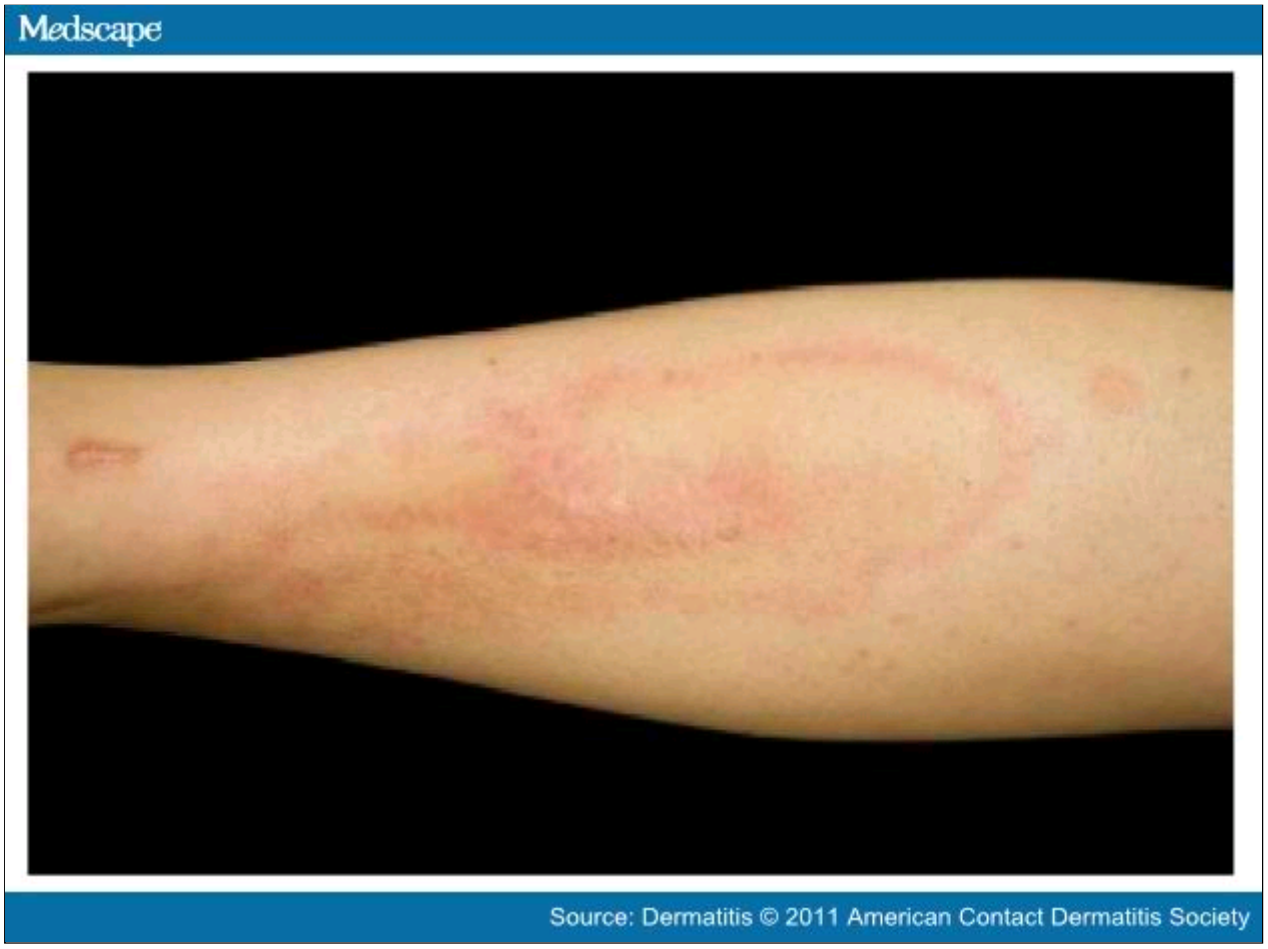

Figure 1. The shin of a woman with dermatitis adjacent to implanted titanium orthopedic hardware. Pathology examination revealed perivascular and periadnexal lymphoeosinophilic infiltrates consistent with hypersensitivity reaction. This resolved within 3 weeks of the hardware's removal.

A non-exhaustive summary of reported cases of cutaneous reactions caused by a metallic implant is given in Table 5. Although many of the patients were patch test positive to their implanted metals, it is important to note that several were patch test negative. Although neither lymphocyte transformation test results nor serum metal levels were reported in these cases, those examinations may be useful in confirming metal allergy in these types of patients. The temporal and physical evidence before and after removal of the implants leaves little doubt that a considerable number of patients develop metal sensitivity and cutaneous allergic dermatitis in association with metallic orthopedic implants.

Table 5. Cutaneous Reactions after Insertion of a Metallic Orthopedic Implant*

Authors	Ref. No.	Patients	Procedure	Clinical Symptoms or Signs	Time to Appearance	Management and Outcome	Patch-Test Reactions
Thomas et al	8	37-year-old female s/p fracture of right wrist	Reduction and insertion of vitallium plate	Oozing, irritation around scar initially, then extended to right forearm and	10 weeks post surgery	Rash resolved after plate removal	Nickel +++

				hands			
							Cobalt +++
Merle et al	19	57 M s/p fracture of left knee	Osteotomy with insertion of vitallium plate and screws	Generalized eczema	3 mo post surgery	Topical therapy unsuccessful; rash resolved after plate and screws removed	Cobalt ++
Rostoker et al	24	27 M s/p fracture of left tibia	Sherman plate (stainless steel alloy Al316)	Generalized eczema	7 mo post surgery, for 7-yr duration	Rash resolved within 1 mo of hardware removal	Nickel +++
Rostoker et al	24	56 F s/p fracture of left tibia	Intramedullary nail (stainless steel alloy Al316)	Generalized eczema	12 mo post surgery	Rash resolved within 15 days of hardware removal	Negative
		28 M s/p fracture of left clavicle	Osteosynthesis with screw (stainless steel alloy Al316)	Generalized urticaria	12 mo post surgery	Topical therapy unsuccessful; rash resolved within 1 mo of hardware removal	Negative
Kanerva and Forstrom	25	35 M s/p fracture of right ankle	Surgical realignment, metal plates & screws (made of Fe, Cr, Ni)	Eczema on hands	1 mo post surgery	Rash improved with hardware removal, but quickly relapsed	Nickel +++
							Budesonide +++
							Chromate +
Verma et al	118	15 patients (13 F, 2 M; 65–80 yr)	TKA	Localized eczema	1–3 mo post surgery	Rash resolved with topical steroids	Nickel + (4/15)
							Chromium + (2/15)
							Cobalt + (1/15)
Thomas et al	27	35 F s/p fracture of right tibia	Open reduction and plate fixation	Localized eczema	A few weeks post surgery	Ongoing eczema due to remaining metal fragments after plate removal	Nickel ++
							Cobalt +

Carboni et al	28	6 patients (53–72 yr)	PCA prostheses (4 hip, 1 knee, 1 patella removal)	Itching, pain (4 patients)	A few months post surgery	Not available Nickel	Nickel +++ (3/6)
				Eczema (2 patients))			Cobalt +++ (3/6)
							Imidazolidinylurea +++ (1/6)
							Ethylenediamine chlorhydrate (1/6)
Carboni et al	28	3 patients (45–70 yr)	ABG hip prostheses	Itching, burning	Not available	Not available	Negative
Carboni et al	28	2 patients (63 and 34 yr)	Arthroimmobilization	Diffuse eczema	Not available	Not available	Negative (1/2)
			Osteosynthesis with A0 prostheses				Nickel, cobalt +++ (1/2)
		73-yr-old with fractured leg	Left-leg prosthesis (acrylic cement) and potassium dichromate	Diffuse eczema	6 mo post surgery	Eczema completely resolved after prosthesis removal	Positive for certain allergens in the acrylic cement and for potassium dichromate
Ridley	29	78 F with OA	TKA with metal-onplastic prosthesis (Co-Cr alloy)	Initial localized swelling and pain	2 mo post surgery	Not available	Not available
				Eczematous reaction while being treated with antibiotics			
Symeonides et al	30	30 M s/p fracture of right humerus	Open reduction and internal fixation with vitallium plate and screws	Generalized urticaria	2 mo post surgery	Urticaria completely resolved within 3 days of hardware removal	Nickel +
Gao et al	119	62 M with OA	TKA, Co-Cr-Mo alloy	Generalized eczema	6 mo post surgery	Eczema resolved within 2 mo of revision to zirconium-niobium alloy prosthesis	Chromium ++++
Handa et al	120	57 M	Total knee replacement with condylar knee	Exudative dermatitis	2 mo post surgery	Not available	Cobalt +
							Copper sulfate +

							Nickel −
Beecker et al	121	48 F with bilateral OA and allergy to Ni and Co	Bilateral TKA	Eczematous dermatitis that became generalized	1–2 mo post surgery	Skin findings managed with topical steroids, with good response	Nickel +++
							Cobalt +++

ABG = Anatomique Benoist Giraud; Co = cobalt; Cr = chromium; F = female; Fe = iron; M = male; Mo = molybdenum; Ni = nickel; OA = osteoarthritis; PCA = porous coated monatomic; Ref. = Reference; s/p = status post; TKA = total knee arthroplasty.
*List may not be exhaustive.

Noncutaneous complications involving orthopedic implants may occur following total hip or knee arthroplasty as well as following the insertion of other dynamic implants. Cases of noncutaneous reactions believed to be caused by metal hip and knee implants are summarized in Table 6 and Table 7. First-generation metal-on-metal orthopedic hip bearings were introduced in the 1960s and 1970s and were associated with high rates of metal release and sensitization (28–46%).[11,32] The prostheses resulted in the excessive release of cobalt, nickel, and chromium into the blood, hair, and urine.[33,34] Metal-on-plastic implants, which were increasingly used from the 1970s through the 1990s, are less likely to induce metal sensitization because they release large polyethylene wear particles that prevent the formation of allergenic polymer-protein complexes.[13,35]

Table 6. Cases of Aseptic Lymphocytic Vasculitis–Associated Lesions after Hip Arthroplasty*

Authors	Ref. No.	Patient	Procedure	Clinical Symptoms and Signs	Time to Onset	Management and Outcome	Periprosthetic Fluid Analysis and Biopsy Result
Mikhael et al	122	53 M	Bilateral MOM arthroplasty	Bilateral hip pain, intermittent lowgrade fever	Pain at time of surgery; persistent for 3 yr	Exchange of metal liner with cross-linked polyethylene liner led to resolution of pain and fever within 8 mo.	ALVAL
		55 M	Left MOM THR	Pain, swelling, limping	3 mo post surgery	Implantation of cross-linked polyethylene bearing surface led to symptom resolution in 3 mo.	ALVAL
Campbell et al	123	53 F	MOM hip resurfacing with Co-Cr alloy	Groin pain	4 mo post surgery	Revision to titanium THR with ceramic-on-ceramic bearing led to symptom resolution.	ALVAL
		47 F	MOM hip resurfacing with Co-Cr alloy	Groin pain, locking sensation, swelling	3 mo post surgery	Revision to cementless total hip with ceramic-onceramic bearing led to symptom resolution.	ALVAL
		54 M	Bilateral MOM hip resurfacing	Groin pain	1 yr post surgery	Revision to a ceramic-on-ceramic THR led to symptom resolution.	ALVAL

		56 M	MOM hip resurfacing	Groin pain	4 mo post surgery	Revision to titanium alloy with ceramic-on-ceramic bearing led to symptom resolution.	ALVAL
Jensen et al	124	71 F	THA, Co-Cr based	Groin pain	Months after surgery	Normal pelvic radiography. CT scan showed cystic collection of fluid with negative leukocyte scintigraphy. Large periprosthetic cystic mass removed surgically.	ALVAL
Counsell et al	125	40 F	Bilateral hip replacements	Lump in left groin associated with shooting pain	12 mo post surgery	Surgical exploration; pending revision.	ALVAL

ALVAL = aseptic lymphocytic vasculitis–associated lesions; Co = cobalt; Cr = chromium; CT = computed tomography; F = female; M = male; MOM = metal-on-metal; Ref. = reference; THA = total hip arthroplasty; THR = total hip replacement.
*List is not exhaustive.

Table 7. Other Cases of Metal Reactions following Hip or Knee Arthroplasty*

Author	Ref. No.	Patient	Procedure	Clinical Symptoms and Signs	Time to Onset	Management and Outcome	Periprosthetic Fluid Analysis and Biopsy Results
Pandit et al	126	50 F	Bilateral MOM hip resurfacings (34 mo apart)	Hip pain	6 weeks post 2nd surgery	Revision to conventional THR led to resolution of pain.	Pseudotumor posterior to joint
		64 F	Bilateral hip arthroplasty	Groin pain; lump under scar	58 mo post surgery	Symptoms controlled with repeated joint aspirations.	Bilateral pseudotumors
		47 F	Bilateral hip arthroplasty	Bilateral hip pain	2 mo post 2nd surgery	Revision on one side. led to symptom resolution; awaiting revision on other side.	Bilateral pseudotumors anterior to joints (10 mo apart)
		65 F	Bilateral hip arthroplasty	Hip pain; femoral nerve palsy	6 mo post 2nd surgery	Staged revision resulted in pain relief, but nerve palsy did not recover.	Pseudotumors posterior to joints (4 mo apart)
Pandit et al	127	35–73 F (17 pts)	MOM hip resurfacings	Pain (15/17); lump (6/17); nerve irritation or palsy (5/17); dislocation (2/17); instability (2/17); rash (1/17); none (2/17)	Mean: 17 mo post surgery (0–66 mo)	13/17 underwent revisions to conventional THR; 8/13 with improved symptoms; 4/13 with complete resolution; 2/17 awaiting revision; 3/17 coping well.	Pseudotumors

Benevenia et al	128	63 M	Cementless TKR	Dull aching pain, swelling, followed by supracondylar fracture	6 yr post surgery	Surgical exploration, revision to LCS prosthesis with bone graft and PMMA cement.	Pseudotumor posterolateral to the joint
Dietrich et al	129	57–68 F (4 pts) with metal allergy	TKA with Co-Cr-Mo–based endoprostheses	Erythema, swelling, sterile effusions, pain with limitation of movement	Months to years post surgery	Changed to titaniumplated endoprostheses; symptoms resolved.	None

Co-Cr-Mo = cobalt-chromium-molybdenum; LCS = low contact stress; MOM = metal-on-metal; PMMA = polymethylmethacrylate; pts = patients; Ref. = reference; THR = total hip replacement; TKA = total knee arthroplasty; TKR = total knee replacement.
*List is not exhaustive.

Recently, second-generation metal-on-metal bearings were introduced. Such prostheses have a lower volumetric wear rate, high fracture toughness, and the ability to use large femoral heads, which may decrease the risk of postoperative instability.[36] These bearings are typically used with younger patients. However, a few studies have documented elevated serum and urine concentrations of cobalt and chromium as seen with first-generation metal-on-metal hip bearings.[36–40] A recent case-control study comparing the prevalence of complications following hip arthroplasty in patients with and without a previous metal allergy found no overall difference.[41] Also, clinically serious complications with aseptic lymphocytic vasculitis– associated lesions and pseudotumors have been reported, typically in association with metal-on-metal bearings (see Table 6 and Table 7).

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*List is not exhaustive.

To what degree metal sensitivity contributes to implant failure remains highly controversial. Thomas and colleagues[42] studied a cohort of 16 patients with failed metal-on-metal arthroplastic implants; 81% of the patients were found to have metal sensitivity (defined as a positive patch-test reaction or positive lymphocyte transformation test result or both), suggesting that metal hypersensitivity may be contributing to the failure of metal-on-metal arthroplastic implants. Reed and colleagues[43] studied 44 patients, 22 of whom had a history of metal reactions evaluated prior to metal implantation and 22 of whom had the following symptoms following implantation: unexplained skin eruptions at the implantation site (13 patients), chronic joint pain (8 patients), and joint loosening (1 patient). None of the symptomatic patients had had positive patch-test reactions to a component of the implanted device. In the preimplantation group, 5 of 22 patients had metal sensitivity, resulting in avoidance of the material in the implant. The authors suggested that preimplantation patch testing might be useful for evaluating the cases of those patients who have a reported history of metal sensitivities. Savarino and colleagues[44] examined 59 patients who had total knee replacements (24 stable and 35 loosened) and compared their measured serum levels of aluminum, titanium, chromium, and cobalt ions to those of 41 healthy controls. Chromium ion levels were significantly elevated (p = .001) in those with loosened implants. The other metal ions were not significant.

Accumulated reports of metal allergy in total hip arthroplasty patients showed that the prevalence of metal allergy was approximately 25% among patients with a well-functioning hip arthroplastic implant and 60% among patients with a failed or poorly functioning implant.[9] Despite these prevalences' being much higher than general population estimates, it is uncertain whether metal allergy causes device failure or whether device failure causes metal allergy.

Allergic Contact Dermatitis from Bone Cement Components

Allergic contact dermatitis from bone cement components may also occur and was reported in 24.8% of patients in one series (n = 239).[45] Most orthopedic bone cements are composed of methyl methacrylate (MMA), N,N-dimethylp-toluidine (DPT), and benzoyl peroxide.[46] Antibiotics (gentamicin being the most prevalent) are often added to the cement. These cements may contain tobramycin, clindamycin, and erythromycin.[46] DPT may be a significant cause of aseptic loosening. In one series, 7 of 15 patients with aseptic loosening of a total hip replacement were DPT allergic.[47]

Although MMA is a known allergen for orthopedic and dental workers, the relevance of MMA as a cause of allergy in joint replacement is not well defined in the literature. In one study, a single series of 42 patients was patch-tested with MMA 6 months after hip arthroplasty; 25% of this cohort had positive reactions to MMA.[48]

The most common components that cause potential orthopedic joint symptoms and potential failure are listed in Table 8. The addition of these agents to any screening patch test is recommended.

Table 8. Common Bone Cement Allergens Used in Total Joint Arthroplasties

Allergen	Reference No.	Use	Approx. % Positive Reactions
N,N-Dimethyl-p-toluidine	47	Reaction initiator	10

Polymethyl methacrylate (MMA)	48	Cement base	25
Benzoyl peroxide	117, 130	Activator	8–10
Hydroquinone	117	MMA stabilization	5
Gentamicin	130	Antibiotic	17–24

Allergic Contact Dermatitis from Dental Implants and Prostheses

Cases of allergic contact dermatitis in association with dental implants have also been reported.[9,11,13,49–56] In 1966, Foussereau and Langier[23] reported a case of generalized dermatitis in the setting of a chromium-nickel denture. Patch testing elicited a strong reaction to nickel and chromium in this patient. The skin eruption resolved completely after the denture was removed. Hubler and Hubler[11] reported a similar case of generalized eczema following the placement of a denture plate that contained a chromium-cobalt alloy. Removal of the dental plate cleared the eruption, but the eruption reappeared within 24 hours of the denture plate's reinsertion. Pigatto and colleagues[56] described a 48-year-old atopic woman who developed generalized eczematous dermatitis after the placement of titanium dental implants and (later) a dental prosthesis containing chromium-cobalt alloy. Patch testing revealed allergies to dental amalgam, nickel sulfate, and palladium chloride.

Allergic contact dermatitis from dental implants may present differently in individual patients. The most frequent manifestation is a lichenoid reaction characterized by oral lichen planus–like lesions. The lesions may be reticular, atrophic, erosive, or plaquelike and usually abut the eliciting implant. Lichenoid reactions have been reported in association with dental amalgams and gold.[57]

Mercury amalgams, the most commonly used restorative material in dental practice, release large quantities of mercury ions. Mercury ions are the most frequent potential allergens that induce a cell-mediated DTH reaction. Other metals (including copper, zinc, palladium, cobalt, and tin) have also been implicated in eliciting contact allergy. Lichenoid reactions due to gold sensitization have been reported, albeit less frequently.[58–64] The use of amalgam fillings has been largely abandoned in recent years.

Gold allergy is common in patch-tested patients who have dermatitis; in one series, its rate approximated nickel allergy rates.[65] In another series of asymptomatic patients with gold restorations, 24 of 71 (33.8%) patients with gold restorations had a patch-test positive reaction to gold, as opposed to 7 of 65 (10.8%) "nongold" patients.[66] This highlights the need for assessment of the clinical relevance of gold patch test–positive results. Most individuals with hypersensitivity to gold (as confirmed by patch testing) are able to tolerate dental restorations that contain gold.[61,63,66–68]

Finally, dental restorations that contain nickel are associated with low rates of intraoral nickel-induced allergic reactions.[69–71] Removal of the dental implant has resulted in healing of the lesions within days or weeks in 49 to 95% of cases, which suggests a cause-effect relationship between the implant and the particular reaction.[69,72] Nevertheless, a few reports have shown that patients with a known nickel allergy as confirmed by patch testing do not develop oral complications in the setting of nickelcontaining dental restorations.[71,72] Oral tolerance may occur in subjects exposed to nickel from dental braces.[73]

Amalgam tattoos are another manifestation of mercury-related intraoral contact allergy.[72,74] They occur when small particles of dental amalgam get implanted into the oral soft tissues during dental procedures. Amalgam tattoos appear as blue, black, or gray asymptomatic patches on the oral mucosa. Burning mouth syndrome (BMS) and "burning lips syndrome" (a subtype of BMS) have been reported in association with strong allergy to cobalt, nickel, mercury, and gold.[58,59,75–80] Patients with BMS seem to have a higher frequency of contact allergy to gold than to mercury. In some cases, patients recovered completely after the removal of the mercury amalgam filling or dental gold. Also, an association between the use of DPT in bone cement and burning mouth reactions is seen in some patients.

Allergic Contact Dermatitis and In-stent Restenosis from Vascular and Cardiac Implants

Allergic contact dermatitis (ACD) and device failure may occur in response to implanted intravascular metal exposures. This topic was extensively reviewed recently by Honori and colleagues.[12]

Percutaneous transluminal coronary angioplasty and stent placement are becoming an increasingly common and effective method for the treatment of atherosclerotic disease. There are two main types of stents: bare metal stents and drug-eluting stents. Bare metal stents are composed of different alloys (typically with a backbone of stainless steel), which

are the potential allergens for stent-induced ACD. It is thought that the composite metallic ions induce the expression of intercellular adhesion molecule 1 (ICAM-1) on endothelial cells. This in turn stimulates the recruitment of inflammatory cells and causes excessive neointimal hyperplasia. The proliferative neointimal response is responsible for intraluminal restenosis. Drug-eluting stents, on the other hand, are coated with polymers impregnated with a drug that inhibits intimal hyperplasia and subsequently yield a lower rate of DTH.

Nickel, chromate, manganese, and molybdenum eluted from stainless steel stents are, among the various metals, the most frequent allergens that induce ACD. Contact allergy to these metal ions is also thought to play a role in intraluminal restenosis. Table 9 [81–87] summarizes relevant studies evaluating restenosis. These studies cannot confirm a correlation between metal allergy and restenosis after initial stent implantation. At present, the exact relation between metal allergy and in-stent restenosis remains debatable.

Table 9. Studies Evaluating In-Stent Restenosis*

Authors	Reference No.	Total Patients	Conclusions
Koster et al	81	131	Prospective: 171 total stents; in-stent restenosis in 100% of patients with positive patch-test result but in only 57% of patients with negative patchtest results; no control group; only significant differences were for nickel and molybdenum.
Iijama et al	82	174	No difference in positive patch-test results between restenosis and nonrestenosis groups after stent implantation (9% vs 10%).
Hillen et al	83	34	Restenosis occurred predominantly in patients with negative patch-test reaction to nickel.
Norgaz et al	84	43	Patch-tested at time of stenting and again in 6 mo; 6.9% were nickel allergic, but 37% developed instent restenosis; 1/3 nickel-allergic patients developed diffuse in-stent restenosis.
Saito et al	85	> 1 stenosis = 60 (case) 1 stenosis = 68 (control)	Bare metal stainless steel 316L stents; 19% (24/128) of all patients were nickel positive; "24 nickel positives, 30% in study group, 9% in control group (p = .02)."
			Multivariate analysis: most significant predictor of chronic in-stent restenosis: reference vessel diameter (p = .0010), nickel positive (p =.0033), hyperlipidemia (p = .0305).
			Highest odds ratio for restenosis (5.41) were in nickel positives.
Hansen et al	86	10	No metal allergy was found in 10 patients with very late in-stent restenosis.
Svedman et al	87	338	Nickel-stented patients: difference in restenosis rate between "allergic patients with restenosis (n = 8, 17.8%) and not allergic with restenosis (n = 36, 12.3%) was not statistically significant (p > .3)."

*List may not be exhaustive.

Gold-coated stents were developed because gold (due to its higher stability) was thought to be less allergenic than the aforementioned metals. The frequency of contact allergy to gold was reported to be 5 to 10% in patch-tested patients with eczema.[88] Nevertheless, studies showed a higher risk of gold contact allergy in patients with goldplated endovascular stents.[89–92] Furthermore, the rate of restenosis was greater among patients with gold-plated stents than among those with stainless steel stents although this was statistically insignificant.[93,94] For these reasons, gold-plated stents are rarely used at this time.

Allergic reactions to patent foramen ovale (PFO) occluders have been reported, although rarely. The Amplatzer occluder (AGA Medical Corporation, Plymouth, MN), the only such device approved by the US Food and Drug Administration, is made of nitinol (approximately 45% nickel) and releases nickel; however, its effect on surrounding human tissue has not

been studied. To date, only three patients have been reported to develop systemic allergic reactions to PFO occluders without apparent rash but with positive patch-test results.[95–97] Each of these patients' symptoms improved following either the removal of the device or the use of systemic corticosteroids.

Anecdotal reports of ACD from endovascular devices used for repair of an abdominal aortic aneurysm (AAA) are rare. Gimenez-Arnau and colleagues[98] reported the first case, that of a patient who developed generalized eczematous dermatitis 3 weeks after undergoing an AAA repair with a straight Vanguard endograft. This was thought to be due to the nickel contained in the endograft (the patient had a positive patch-test reaction to nickel). The patient responded well to systemic antihistamine and topical corticosteroid therapy.

The first implantable pacemakers were developed in the 1960s.[12] Pacemaker generators are made most frequently of titanium because of titanium's high biocompatibility. Other metals, including nickel and silicone, are also used, although in smaller amounts. The first case of pacemaker contact dermatitis was reported in 1970; since then, a growing number of cases have been documented.[99–107] Titanium is the most common allergen; nickel and silicone are other potential allergens. According to many reports, the use of a polytetrafluoroethylene (PTFE) sheet to wrap the device has been successful in preventing the recurrence of dermatitis during the reported follow-up periods of up to 3 years.[104,107–109] Recently, Ishii and colleagues[100] described the case of a 52-year-old man with Down syndrome who received a dual-chamber paced, dualchamber sensed, dual response rate moderated (DDDR) pacemaker for advanced atrioventricular block and developed cutaneous eczema and partial exposure of the generator 1 year after reimplantation. His patch-test result was positive for the metal of the generator (99.9% titanium) after 72 hours. The patient was subsequently reimplanted with a pacemaker wrapped with a PTFE sheet; 3 years later, the dermatitis had not recurred. Replacement with customized silicone or gold-coated pacemakers has also been reported to resolve pacemakerinduced allergic dermatitis; however, success rates are lower than those achieved with PTFE.[105,106,110]

Allergic Contact Dermatitis from Gynecologic Implants

Copper, nickel, and titanium are used in several devices for female contraception. Copper sulfate–containing intrauterine devices placed for temporary contraception are rare causes of systemic dermatitis. There are at least three cases of patch test–confirmed systemic ACD that resolved after the removal of a copper-containing intrauterine device.[111–113] A recent development in permanent contraception was the development of a nitinol-containing device for implantation in the fallopian tubes. This device (called Essure in the United States [Conceptus Incorporated, Mountain View, CA]) is implanted during an in-office transvaginal procedure into women desiring permanent contraception.[114] A contraindication to placement is previous nickel allergy. Likely, this contraindication is due to nickel release from the nitinol alloy, causing a potential systemic ACD. All prospective users of this device should be patch-tested with nickel prior to placement. The authors believe that nickel should not be used in such devices.

Conclusions

Most information regarding putative sensitivity reactions to endovascular, cardiovascular, orthopedic, and dental metal implants are based either on anecdotal case reports or on data gathered from relatively small cohorts. Very few prospective data are available. For decades, it was believed that only selected highly susceptible patients (< 1%) developed skin complications due to metal implants; however, a recent case study showed that a significantly higher number of patients (5%) developed eczematous reactions directly associated with metallic implants.[21] Those individuals with a preexisting metal sensitivity who receive an implant containing the offending metal had a higher rate of cutaneous dermatitis compared to those without metal allergy. Another study examining this exact situation suggests that there may be no adverse reactions to implanting the allergenic metal.[115] Further prospective and well-powered studies are needed to definitively answer this question.

In the majority of cases, the removal of the allergenic metal device results in clearing of the skin condition. Based on these data, we recommend that patients who develop a cutaneous eruption months to years after receiving a metal implant should be patch-tested with an appropriate series of metals. If relevant allergens are identified and corticosteroid therapy is insufficient to clear the eruption, removal of the implant may be considered. A perfectly functioning dynamic implant causing no pain and without evidence of loosening should not be removed in most cases, despite a positive patch-test result.

Although removal of offending devices may clear the dermatitis, prevention of reactions and complications is preferable. There is no general support for preimplantation patch-test evaluation, but it may be considered for individuals who are suspected of having a strong metal allergy. One study suggested that patients with a history of metal reactions prior to

implantation may have an increased risk of arthroplasty failure, but this study had methodologic limitations.[16] In comparisons of 22 individuals before, and 22 individuals after, the implantation of orthopedic devices, 5 individuals were identified as being allergic to the alloy in their proposed device, whereas none (0 of 22) of the symptomatic individuals had positive reactions when tested.[43] Another approach was suggested by Carlsson and Moöller, who reported that no patients had adverse reactions to metal implants to which they were sensitized prior to implantation,[20] and by Bruze, who reports that no preimplantation testing is performed in Sweden.[116] The reason some patients develop cutaneous complications in association with metal implants and others do not remains a puzzle. Prospective longitudinal studies are strongly needed to shed further light on this subject. We also need better insight into the diagnostic performance of patch testing and in vitro test methods.

It is hoped that our knowledge about the associations between metal allergy, allergic contact dermatitis, and device failure will expand. At present, it is unknown whether the risk of device failure and allergic contact dermatitis is increased in metal-allergic persons. With aging populations in Western Europe and the United States, there is an urgent need for greater insight. The use of metal implants is expected to grow rapidly. At the same time, the generations of people who became metal allergic in great numbers from the 1960s to the 1980s either from industrial metal exposure or from exposure to consumer products and cosmetic procedures (such as wristwatches, jean buttons, inexpensive jewelry, and ear piercing) are gradually aging. As dermatologists are often consulted about the possible role of metal allergy in patients awaiting implantation, this collision course warrants our full attention.

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