REVIEW

Hypersensitivity Reactions to Titanium: Diagnosis and Management

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Titanium is notable for its biocompatibility and is used as biologic implant material across surgical specialties, especially in metal-sensitive individuals. However, rare cases of titanium hypersensitivity reactions are reported in the literature. This article discusses the properties and biological behavior of titanium and provides a thorough review of the literature on reported cases, diagnostic techniques, and approach to management of titanium hypersensitivity.

Titanium was first discovered in 1791 as a unique anatomic element and later named for the Greek mythological God, Titan, in 1795. However, it was not successfully purified on a large scale until 1910, and widespread industrial use followed in the mid-1900s. Originally utilized solely in tactical military and aerospace applications, titanium is now used in diverse products such as sports equipment, medical devices, pharmaceuticals, plastics, paint, jewelry, cosmetics, sunscreens, candy, and toothpaste.[1]

Many experts consider titanium as the non-allergenic metal of choice for biologic devices, especially in metal-sensitive individuals. However, recent data suggest that there may be rare cases of titanium hypersensitivity. This article discusses the properties and biological behavior of titanium and provides a thorough review of the literature on reported cases, diagnostic techniques, and approach to management of titanium hypersensitivity.

Properties of Titanium and Its Alloys

This lustrous transitional metal is renowned for its high strength-to-weight ratio, low modulus of elasticity, corrosion resistance, and biocompatibility. It exists in 2 configurations: (1) α type (hexagonal crystalline structure) at room temperature and (2) β type (body-centered cubic crystalline structure) with a phase transition temperature of 882°C. Titanium (Ti) is classified as either commercially pure titanium (CpTi) or a titanium alloy (Table 1).[2,3] Commercially pure titanium has tensile strength equal to that of low-grade stainless steel, yet it is 45% less dense. Grade 2 CpTi (99.3% pure) is overwhelmingly the most popular in medical device production.[4] It is important to recognize that all CpTi has been shown to contain a small yet consistent percentage of detectable impurities, such as the elements aluminum (Al), beryllium (Be), cadmium(Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), hafnium (Hf), manganese (Mn), molybdenum (Mo), nickel (Ni), palladium (Pd), and vanadium (V).[5] The presence of these trace elements is believed to be negligible from a metallurgical standpoint but may potentially be significant enough to cause an allergic reaction in an already sensitized patient.

Alloys

Alloy elements may be added to Ti to manipulate its properties for optimum performance. Alloy elements can be classified into α stabilizers, β stabilizers, and α + β stabilizers (Table 1).[2,3] Increasing the α-phase improves weldability and high-temperature stability, whereas increasing the β-phase increases room temperature strength and enhances the durability of medical device implants. Currently, commercially pure titanium and α + β–type noble (precious metal) alloys, such as Ti-6Al-4V ELI (extra low level of interstitial content) are widely used for medical and dental implant materials. More recently, vanadium-free alloys have been developed (Ti-6Al-7Nb and Ti-5Al-3Mo-4Zr), which exhibit equally good mechanical properties. In addition, more cost-effective nonnoble alloys such as Ni-Ti (NITINOL [NITINOL was named for its elemental components and place of origin: NIckel TItanium Naval Ordinance Laboratory]) and Ti-Co have also been developed.[4]

Oxidation

Upon exposure to air, pure titanium and its alloys oxidize immediately, creating a 1- to 2-nm thick oxide layer that protects the bulk metal from further redox reactions. This passivating layer mainly consists of titanium dioxide (TiO_2), and it contributes to titanium's anticorrosive properties. It is notable that 95% of the global use of titanium is actually not in its metal form, but

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The authors have no funding or conflicts to declare.

This material is the result of work supported with resources and the use of facilities at the Minneapolis Veterans Affairs Medical Center. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US Government.

DOI: 10.1097/DER.0000000000000091

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TABLE 1. Titanium and Its Alloys

ASTM Grade	Description	Comments
Commercially pure unalloyed titanium (α phase)		
1	99.5% Pure, low oxygen content	
2	99.3% Pure, medium oxygen content	Most frequently used CpTi grade in dental and medical industry
2H	Grade 2 with 58 ksi (400 MPa) minimum UTS	
3	99.2% Pure, high oxygen content	Least popular in all industries due to poor corrosion resistance
4	99.0% Pure, extra-high oxygen content	Serves mainly in aerospace/aircraft industry, some dental implants
Commercially pure modified with palladium or ruthenium (α phase)		
7	99.4% Pure, plus 0.12%-0.25% palladium	
7H	Grade 7 with 58 ksi (400 MPa) minimum UTS	
11	Unalloyed titanium plus 0.12%-0.25% palladium	
16	Unalloyed titanium plus 0.04%-0.08% palladium	
16H	Grade 16 with 58 ksi (400 MPa) minimum UTS	
17	Unalloyed titanium plus 0.04%-0.08% palladium	
26	Unalloyed titanium plus 0.08%-0.14% ruthenium	
26H	Grade 26 with 58 ksi (400 MPa) minimum UTS	
27	Unalloyed titanium plus 0.08%-0.14% ruthenium	
α And near-α alloys		
α Stabilizers: Al, Sn, Ga, Zr, C, O, N		
12	Ti-0.3Mo-0.8Ni	
6	Ti-5Al-2.5Sn	
	Ti-5Al-5Sn with ELI	
9	Ti-3Al-2.5 V	
18	Ti-3Al-2.5 V, plus 0.04%-0.08% palladium	
28	Ti-3Al-2.5 V, plus 0.08%-0.14% ruthenium	
	Ti8Al-1Mo-1 V	
	Ti-6Al-2Nb-1Ta-0.8Mo	
	Ti-2.25Al-11Sn-5Zr-1Mo	
	Ti-5.8Al-4Sn-3.5Zr-0.7Nb-0.5Mo-0.35Si	
α + β Alloys		
5	Ti-6Al-4V	Widely used in dental and medical industry
23	Ti-6Al-4V-ELI	Widely used in dental and medical industry
24	Ti-6Al-4V, plus 0.04%-0.08% palladium	
25	Ti-6Al-4V, plus 0.3%-0.8% nickel and 0.04%-0.08% palladium	
29	Ti-6Al-4V-ELI, plus 0.08%-0.14% ruthenium	
	Ti-6Al-7Nb	Developed as a substitute for Ti-6Al-4V due to vanadium's potential biotoxicity
	Ti-5Al-3Mo-4Zr	
	Ti-6Al-6 V-2Sn	
	Ti-8Mn	
	Ti-7Al-4Mo	
	Ti-6Al-2Sn-4Zr-6Mo	
	Ti-5Al-2Sn-2Zr-4Mo-4Cr	
	Ti-6Al-2Sn-2Zr-2Mo-2Cr	
	Ti-3Al-2.5 V	
	Ti-4Al-4Mo-2Sn-0.5Si	

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TABLE 1. ***(Continued)***

ASTM Grade	Description	Comments
β Alloys		
β Stabilizers: V, Mo, Nb, Ta, Cr		
19	Ti-3Al-8 V-6Cr-4Zr-4Mo	
20	Ti-3Al-8 V-6Cr-4Zr-4Mo, plus 0.04%-0.08% palladium	
21	Ti-15Mo-3Al-2.7Nb-0.2Si	
	Ti-10 V-2Fe-3Al	
	Ti-13 V-11Cr-3Al	
	Ti-8Mo-8 V-2Fe-3Al	
	Ti-3Al-8 V-6Cr-4Mo-4Zr	
	Ti-11.5Mo-6Zr-4.5Sn	
	Ti-15 V-3Cr-3Al-3Sn	
Undesignated alloys		
33, 34	Ti-0.4Ni-0.015Pd-0.025Ru-0.15Cr	
35	Ti-4.5Al-2Mo-1.6 V-0.5Fe-0.3Si	
36	Ti-45Nb	
37	Ti-1.5Al	
38	Ti-4Al-2.5 V-1.5Fe	
39	Ti-0.25Fe-0.4Si	
13, 14, 15	Ti-0.5Ni-0.05Ru	
30, 31	Ti-0.3Co-0.05Pd	
32	Ti-5Al-1Sn-1Zr-1 V-0.8Mo	
	Ni-Ti	Also known as NITINOL

ksi Indicates 1000 pounds per square inch; UTS, ultimate tensile strength; ELI, extra low interstitial elements; NITINOL, NIckel TItanium Naval Ordnance Laboratory.

rather as TiO_2 powder for its whitening effect, sunscreen properties, and use as a safe excipient in cosmetic, pharmaceutical, and food industries.

Metal Hypersensitivity

Metal hypersensitivity is typically characterized as a type IV hypersensitivity reaction, with a sensitization phase upon first exposure followed by an elicitation of an immune response on subsequent exposure of sufficient concentrations. In order to become allergenic, metal ions require binding with native proteins to form antigenic hapten complexes. These complexes are then processed by antigen-presenting cells and presented to T cells.[7] Sensitization typically occurs through contact with skin but could also theoretically occur through systemic exposure via ingestion or corrosion of a metal implant.[6,8] The elicitation phase classically presents as a cutaneous allergic contact dermatitis, manifesting in the skin as dermatitis with pruritus, edema, and erythema in mild cases and vesicle and bullae formation in more severe cases.

Hypersensitivity to metal in the general population is common, affecting up to 15.5% of patch-tested patients in North America[9] and up to 20% in Western Europe.[10] The biggest offender is nickel, followed by cobalt and chromium. It is postulated that sensitivity to nickel develops from cutaneous exposures to common everyday items, such as belt buckles, fasteners, and jewelry. The significantly higher incidence of nickel sensitivity in women is thought to be attributable to increased jewelry use; the number of piercings is also significantly associated with nickel sensitivity in both genders.[11]

The relationship between preexisting metal sensitivity and implant-related contact dermatitis or implant failure remains unclear and therefore nearly impossible to predict. The exact cellular pathways involved in the elicitation of systemic metal hypersensitivity reactions have not yet been well established; however, reports of abundant macrophages and T lymphocytes and absence of B lymphocytes in recovered tissues surrounding failed metal implants suggest a possible type IV hypersensitivity reaction.[6,12] In addition, increased levels of cytokines such as interferon γ, interleukin 6 (IL-6) and IL-17 have been observed in metal-sensitive patients.[13–15]

Systemic Contact Dermatitis

Systemic contact dermatitis is classically defined as a condition where an individual sensitized to an allergy through the cutaneous route subsequently reacts to contact with the same allergen via a systemic route.[16] Internal contact with metal ions may occur through corrosion of an implanted metal device. A thorough review of more than 55 reported cases of systemic contact dermatitis is described elsewhere.[17] Symptoms of systemic contact dermatitis may manifest as an eczematous rash at the site of previous external exposure (patch test or jewelry adornment site), generalized eczema, hand dermatitis, erythroderma, vasculitis-like lesions, or flexural exanthema (also known as "baboon syndrome").[15,16]

Titanium in the Biologic Environment

Titanium is a nonessential mineral; it is not required for metabolism or growth and does not serve as a cofactor in any known

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human enzymatic process. Although titanium is ubiquitous in the modern world, sensitivity to titanium is exceedingly uncommon. This can be explained by the fact that contact with titanium is almost entirely in its TiO_2 form, which is water insoluble, does not bind to cells or proteins,[18] does not penetrate the skin,[19,20] and is not absorbed by the gastrointestinal tract.

Corrosion

Contrary to the past reputation of titanium as an "inert" metal, it is now well accepted that no metal is completely inert. Corrosion rates for passivated Ti are typically less than 0.02 mm/y, well below the 0.13-mm/y maximum corrosion rate commonly accepted for biomaterial design and application.[21] Corrosion of Ti and Ti alloys releases Ti(IV) ions, as well as vanadium, aluminum, niobium, molybdenum, and trace element ions such as nickel.[21,22] Accelerated corrosion of titanium has been observed in the presence of a number of corrosive species such as hydrogen ions (H^+), sulfide compounds (S^{2-}), dissolved oxygen (O_2), radical oxygen species and chloride ions (Cl^-), all which can be present in the biologic milieu.[23] Like other metal ions, single titanium ions alone are not antigenic; however, titanium ions from corrosion products or salts can bind to cellular and serum human proteins, specifically transferrin and albumin, and create haptenic antigens that elicit immune responses.[17,24–26] The most commonly observed types of titanium corrosion in the biologic environment include mechanical wear processes, physiochemical corrosion, and cellular-gated mechanisms. Dissolved metal ions can accumulate in the tissue surrounding the implants or can be released into circulation and accumulate in distal organs or be excreted by the kidneys.[20,27,28]

Cellular Response

Small particles of TiO_2 (<10 μm) are phagocytized by polymorphonuclear leukocytes, activating the cells that in turn produce highly reactive oxygen metabolites,[29] a fact that can explain recently described bactericidal properties of titanium[30] and, theoretically, accelerated biocorrosion. The phagocytosis of metal wear particles by tissue macrophages induces production of proinflammatory cytokines that may enhance osteolytic activity at the implant-bone interface.[31,32] Titanium ions themselves can directly induce the differentiation of osteoclast precursors toward mature osteoclasts capable of effective bone resorption.[33] Titanium ions have also been shown to have a strong affinity for phosphorylated proteins, which has led researchers to postulate that they may interfere with cell signaling and/or alter forms of self-antigens, thereby causing autoimmune-like activity.[20]Titanium particles have been observed inside macrophage lysosomes in reports of type IV hypersensitivity.[34–36] In addition, cells necessary for the development of type IV hypersensitivity have been found in perivascular tissue adjacent to failed implants[27]; however, this finding has also been reported in patients with asymptomatic implants at routine explantation.[37]

Tissue Response

Once phagocytized, titanium particles can remain in tissues after the macrophages have been surrounded by collagenous tissues and finally perish.[35] Dark, blackish-brown staining of tissues surrounding titanium implants has been reported.[27,38] It is believed that if wear damages the TiO_2 surface, it rapidly reforms (repassivates), producing so much oxide that the surrounding tissues turn black.[39] This dark tissue discoloration has been reported in both well-functioning as well as failed titanium implants and is considered by itself to be harmless.[40] In addition to local release from implants, there have been reports of the deposition of titanium particles in regional lymph nodes. Onodera et al[41] reported a submandibular lymph node with titanium particles 2 years after a mandibular titanium plate implant in a 41-year-old man. Weingart et al[42] documented 12 of 19 dogs with titanium particles in regional lymph nodes 9 months after maxilla/mandible titanium screw implantation.

Titanium Implants

Titanium is routinely used to manufacture implantable metal devices for a wide variety of applications, including dental, orthopedic, and cardiac implants. It is therefore subject to diverse biological microenvironments capable of delivering variable physiologic and mechanical stressors. There are several types of orthopedic implants (Table 2),[43] each with varying potential for biocorrosive stimuli. For example, the dynamic implants of joint replacements have to withstand completely different forces than static implants used for osteosynthesis. Thus, large implant-derived particles (in the nanometer range) are produced exclusively by the mechanical wear process in articular coupling of prostheses and are not observed with osteosynthesis implants. At the same time, both joint replacement implants and osteosynthesis implants are exposed to similar biological activity and electrochemical processes that can lead to ion release.[20] In a recent in vitro oral implant corrosion study, researchers showed that salivary proteins appeared to spontaneously enhance the formation of a passive film layer on the surface of pure titanium implants, resulting in highly stable behavior of the metal.[44] On the other hand, the human stomatognathic system is subjected to varying changes in pH and temperature.[21] This dynamic microenvironment allows for unpredictable conditions that may actually enable biocorrosion.

Detection of Titanium in Serum

Several studies have found that serum metal levels, including titanium, are higher in patients with failed joints as compared with controls. Jacobs et al[45] evaluated 8 patients with failed titanium alloy cementless total knee arthroplasty (TKA) patellar components and found that serum concentrations of titanium were 50 times higher than those in 21 control subjects without implants; a separate cohort of 21 patients with loose total hip arthroplasty (THA) Ti6Al4V implants found that titanium serum levels were twice that of 21 controls.[46] Leopold et al[46] described a patient with

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TABLE 2. Orthopedic Implants

Procedure	Components	Comments
Joint arthroplasty		
THA	Femoral stem is always metal.* Femoral head component may be metal or ceramic. Acetabular cup may be metal, ceramic, polyethylene†, or a metal shell lined with ceramic or polyethylene fixed with or without metal screws.	Articulation may be metal-on-metal, metal on polyethylene or ceramic on ceramic.
Hip resurfacing	Femoral cap and acetabular cup are metal.	Articulation is always metal-on-metal.
TKA	Contoured metal femoral component, metal tibial plate and stem, polyethylene-bearing spacer, polyethylene patellar backing "button."	Articulation is metal on polyethylene.
Unicompartmental knee replacement	Same components of TKA, but limited to medial, lateral, or patellar portion of joint.	Patellar resurfacing alone requires no metal.
Total shoulder arthroplasty	Metal humoral or glenoid component and stem, polyethylene cup fixed with or without metal screws.	Articulation is metal on polyethylene.
Total elbow arthroplasty	Metal stems, polyethylene liner.	Articulation is metal on polyethylene.
Total wrist arthroplasty	Metal radial and carpal components, metal screws, plastic spacer	Articulation is metal on polyethylene.
Total ankle arthroplasty	Talus component is metal; tibial component is polyethylene with metal base.	Articulation is metal on polyethylene.
Total metacarpophalangeal arthroplasty	Metal metacarpal and polyethylene phalangeal components	Articulation is metal on polyethylene or silicone.
Osteosynthesis		
Internal fixation	Metal‡ plates, screws, nails or rods, wires and pins	May be permanent or routinely explanted
External fixation	Metal pins and wires attached to an external device	Always explanted
Arthrodesis		
Joint fusion	Metal pins, plates, screws, or rods	

** The type of metal used in joint arthroplasty is most commonly a cobalt-chromium alloy.*
† Highly cross-linked polyethylene is a durable and wear-resistant plastic material.
‡ The type of metals used in fixation devices and arthrodesis are typically stainless steel or titanium.

a titanium alloy TKA that functioned well for 10 years; because of painless squeaking, the joint was replaced. The explanted artificial joint showed that the polyethylene portion of the patellar component had worn through, causing direct titanium metal wear and corrosion. Titanium serum level at the time of joint removal was 98 times higher than a year earlier, when the joint was asymptomatic.[47] Correlation between serum ion concentration and lymphocyte reactivity has also been demonstrated, suggesting that in vivo metal release may be associated with joint replacement failure.[48]

Diagnostic Testing for Titanium Allergy

Diagnostic testing for titanium allergy has a longstanding, unreliable, and frustrating history. Available diagnostics include the epicutaneous patch test, intradermal tests, lymphocyte transformation test (LTT), lymphocyte migration inhibition, triple assay, and bidigital O-ring test (BiDORT). Although patch testing is accepted as an effective tool for diagnosis of sensitization to certain metals (eg, nickel), its use for detecting titanium sensitivity is not well accepted. Diagnostic testing for titanium sensitivity is complicated by several factors: (1) titanium sensitivity is exceedingly rare in the general population; (2) standard formulations for titanium testing do not exist, and (3) titanium may not behave like other metals in the testing atmosphere.

Patch Test

Patch testing is the most widely used in vivo method to test for type IV sensitivity reactions to potential contact allergens. There are several patch test screening series including the Food and Drug Administration–approved TRUE Test, the American Contact Dermatitis Society's Core Panel,[49] and the European Baseline Series,[50] none of which include titanium. Various extended metal and prosthesis allergen series have been suggested; all include some form of titanium.[51,52] The literature on titanium patch-testing reports an assortment of powders, solutions, and ointments used at varying concentrations, as well as CpTi and Ti alloy sensitivity disks provided by implant manufacturers (Table 3).[7,27,51,53–69]

Positive patch test reactions to titanium materials are extremely rare. This is not surprising, given that TiO_2 (the most common patch test formulation) has been shown not to penetrate the epidermis in healthy[18,70] or even psoriatic skin.[19] Lhotka et al[53] reported positive patch tests to TiO_2 in a group of patients with a history of skin-penetrating surgical skin clips containing titanium. Other researchers reported positive patch tests using unique formulations of titanium. For example, researchers reported that

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TABLE 3. Patch Testing for Titanium Hypersensitivity in Larger Series of Patients

Reference	No. Patients	Patch Test Concentration	No. Positive (%)	Comments
Davis et al,[52] (United States)	1112 Patients suspected of MHS	119 Patients tested with TiO_2 1% pet	0 (0)	2 (1.7%) Irritant reaction
		94 Patients tested with Ti 10% pet	0 (0)	1 (1.1%) Irritant reaction
		904 Patients tested with a Ti alloy disk	8 (0.9)	8 (0.9%) Irritant reaction
Granchi et al,[7] 2006 (Italy)	223 Patients: 66 candidates for THA, 53 with stable THA and 104 with failing THA	TiO_2 2% pet	3 (1.3)	Among Ti-6Al-4V implant failure Ti-positive patients, 45% also patch tested positive to V
Lhotka et al,[53] 1998 (Austria)	184 Patients who had been subjected to an orthopedic operation using metal suture clips	TiO_2 1% pet	4 (2.2)	Suture clips contained 0.001% to 0.315% Ti
Iljima et al,[54] 2005 (Japan)	174 Patients with cardiac stents, 65 of whom experience in-stent restenosis	Ti 20% pet	0 (0)	Most of the cardiac stents were made of stainless steel, containing no Ti
Okamura and Morimoto,[55] 1999 (Japan)	145 Patients suspected of MHS	0.2% $TiCl_4$ sol	1/73 (1.4)	Authors concluded that because positive reactions were seen with 0.2% and 0.1% $TiCl_4$ and 0.2% and 0.1% $Ti(SO_4)$ solution exclusively in patients suspected of having metal allergies and not in healthy volunteers, that these formulations should be recommended for Ti patch testing
		0.1% $TiCl_4$ sol	2/73 (2.7)	
		0.2% $Ti(SO_4)$ sol	1/73 (1.4)	
		0.1% $Ti(SO_4)$ sol	2/73 (2.7)	
		20% TiO_2 oint	0/73 (0)	
	15 Healthy volunteers were tested with various formulations of titanium salts	5% $TiCl_4$ sol	2/2 (100)	
		2% $TiCl_4$ sol	2/2 (100)	
		1% $TiCl_4$ sol	4/13 (30.1)	
		0.5% $TiCl_4$ sol	3/13 (23.1)	
		0.2% $TiCl_4$ sol	0/13 (0)	
		0.1% $TiCl_4$ sol	0/13 (0)	
		5% $Ti(SO_4)$ sol	2/ (100)	
		2% $Ti(SO_4)$ sol	2/2 (100)	
		1% $Ti(SO_4$) sol	4/13 (30.1)	
		0.5% $Ti(SO_4)$ sol	2/13 (15.4)	
		0.2% $Ti(SO_4)$ sol	0/13 (0)	
		0.1% $Ti(SO_4)$ sol	0/13 (0)	
		20% TiO_2 oint	0/13 (0)	
Cancilleri et al,[56] 1992 (Italy)	107 Patients: 66 patients with both successful and failed THAs of various metals and 41 controls with no metal implants	TiO_2 5% pet	1/66 (1.5)	Specific metal(s) in the prosthesis of the Ti-sensitive patient NR. All controls patch-tested negative to Ti
Granchi et al,[57] 2008 (Italy)	94 Patients: 20 candidates for TKA, 27 with stable TKAs and 47 with failing TKAs	TiO_2 2% pet	3 (3.2)	53 Of the patients had Ti-6Al-4V containing TKAs, 24 stable and 29 failing

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Waterman and Schrik,[58] 1985 (the Netherlands)	85 Patients with various metal-to-polyethylene THA implants	TiO_2 5% pet Preoperative Postoperative	 1 (1.1) 0 (0)	The prosthesis of the patient with a positive titanium result contained no titanium
Frigero et al,[59] 2011 (Italy)	72 Patients patch tested before and after TKA or THA	Ti (metal) 10% pet Preoperative Postoperative	 0 (0) 0 (0)	Some of the patch tested patients received a Ti-Al-V alloy component (exact number NR)
Kręcisz et al,[60] 2012 (Poland)	60 Patients: 21 receiving TKAs and 39 receiving THAs	TiO_2 10% pet 60 Preoperative 48 postoperative	 0 (0) 0 (0)	Metal content of implants NR
Müller and Valentine-Thon,[61] 2006 (Germany)	54 Patients who developed clinical symptoms after receiving Ti-based implants	TiO_2 0.1% oint	0 (0)	21 (37.5) Tested positive to Ti on MELISA
Vermes et al,[62] 2013 (Hungary)	54 Patients: 7 patients without implants and no history of MHS, 7 patients without implants and a history of MHS, and 40 cases of patients undergoing THA with no history of MHS	C_4O_8Ti 0.5%, 1% pet and 5% pet	0 (0)	All hip implants contained Ti-6Al-4V alloy stems, Co-Cr femoral heads, and an ultrahigh molecular weight polyethylene acetabular liner in a Ti-6Al-4V alloy shell
Elves et al,[63] 1975 (London)	50 Patients with both successful and failed total joint replacements	$C_4K_2O_9Ti$ 1% sol	0 (0)	Specific metals in prostheses NR
Milavec-Puretić et al,[64] 1998 (Croatia)	40 Patients undergoing a THA revision surgery	Ti (powder)	0 (0)	None of the failed implants contained Ti
Menezes et al,[65] 2004 (Brazil)	38 Patients patch tested before and 2 mo after receiving a fixed orthodontic appliance	TiO_2 1% Before appliance After appliance	 2 (5.3) 0 (0)	Specific metals in appliances NR
Sicilia et al,[66] 2008 (Spain)	35 Patients: 16 with symptoms after titanium dental implant placement or unexplained implant failures + 19 with multiple allergies, or heavily exposed to titanium during implant surgery; 35 controls	Prick: TiO_2 0.1% and 5% pet, and metallic Ti in 0.1% and 5% aq Patch: TiO_2 0.1% and 5% pet, and metallic Ti in 0.1% and 5% aq	7 (20) all also patch positive 9 (25.7), 7 of these 9 also prick positive	All controls negative Specific allergen formulation that induced the positive results to titanium NR
Basketter et al,[67] 2000 (United Kingdom)	30 Patients: 11 with a prior adverse reaction to ATL, 10 who had been previously exposed to ATL with no reaction, and 9 who had never been exposed	10% ATL pet	11 (36.7)	All individuals with previous adverse reactions to ATL had positive patch tests, whereas all others had negative patch tests
Reed et al,[51] 2008 (United States)	44 Patients: 22 candidates for various metallic implants and 22 patients with various failing metallic implants	Metal and prosthesis series Ti alloy disks, and manufacturer-supplied Ti sensitivity disks	0 (0)	Number of patients who received Ti implants NR

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TABLE 3. (Continued)

Reference	No. Patients	Patch Test Concentration	No. Positive (%)	Comments
Lalor et al,[27] 1991 (England)	5 Patients with aseptic loosening of THAs containing a Ti-Al-V alloy component	$C_{28}H_{20}O_{12}Ti$, $Ti(C_{76}H_{48}O_{46})$, TiO_2, and H_4O_4Ti each at 1%, 2% and 5%paraffin	0 (0)	All 5 patients had black debris containing Ti particles in the surrounding tissue at revision surgery
	4 Of the above 5 and 12 controls without metal implants	Metanium ointment (20% TiO_2, 5% H_4O_4Ti, 3% $C_{28}H_{20}O_{12}Ti$, and 0.1% $Ti(C_{76}H_{48}O_{46})$ in silicone paraffin)	2 (12.5)	All controls were negative
Thomas et al,[68] 2009 (Germany)	16 Patients undergoing revision surgery for failing metal-on-metal hip arthroplasty	TiO_2 0.1% (vehicle NR)	0 (0)	Metal content of implants NR

TiO_2 indicates titanium dioxide; $TiCl_4$, titanium chloride; C_4O_8Ti, titanium oxalate; $C_4K_2O_9Ti$, potassium titanium oxalate; $C_{28}H_{20}O_{12}Ti$, titanium salicylate; $Ti(C_{76}H_{48}O_{46})$, titanium tannate; H_4O_4Ti, Ti peroxide; MHS, metal hypersensitivity; pet = petrolatum; sol, solution; aq, aqueous solution; ATL, ammonium titanium lactate; NR, not reported.

2 patients with unexplained THA failures patch tested negative to 12 different typical preparations of titanium, but curiously tested positive to a "napkin cream" called metanium ointment, containing 20% TiO_2, 5% titanium peroxide, 3% titanium salicylate, and 0.1% titanium tannate in silicone paraffin.[27] An 8-year-old atopic girl who needed a dental brace patch tested negative to titanium and TiO_2 10% in petroleum, but tested positive to titanium nitride and titanium oxalate; importantly, the authors raised concerns regarding impurities present in the testing medium.[71]

A routine skin irritancy study involving a novel antiperspirant formulation spawned the investigation of utilizing a new substance for titanium patch testing, a complex titanium salt, consisting of ammonium titanium lactate. This salt appeared to have elicited type IV hypersensitivity reactions in 11 of 23 volunteer subjects with reproducible results upon patch testing later in parallel with 19 negative control volunteers, 10 of whom had been previously exposed to the salt without adverse reactions.[67] In an attempt to establish a standard patch test for titanium, a research group in Japan recommended $Ti(SO_4)$ and $TiCl_4$, both in 0.1% and 0.2% solutions, as useful reagents for titanium skin patch tests. They based this recommendation on the fact that they observed positive reactions in 3 of 145 metal-sensitive patients and negative reactions in 15 healthy volunteers.[55] However, it is well known that metal chlorides are potential irritants even at low concentrations, and positive reactions on patch testing may not represent allergenicity.[72] For example, $TiCl_4$ is the intermediate compound in the production of titanium dioxide, and when mixed with water—even when that water is in the form of perspiration—will generate a vigorous exothermic reaction that yields heat and hydrochloric acid, both of which are sources of potential skin damage.[73] In fact, severe burn injuries have been reported upon exposure to this compound.[72,74,75] It is possible that reported hypersensitivity reactions to a titanium disk with artificial sweat actually represent metal chloride irritant reactions.[76] Currently, there remains no reliable patch test for titanium.

Lymphocyte Transformation Test

The LTT is an in vitro measurement of the proliferation response of lymphocytes following antigen-specific activation. A radioactive [H^3]-thymidine marker quantifies the proliferation response by measurement of the incorporated radioactivity over 5 to 7 days and is reported as a stimulation index (SI). This index is calculated from the quotient of test counts per minute over the average counts per minute from 3 negative controls. An SI of less than 2 is considered negative, SI 2 to 3 suggests possible sensitization and SI of 3 or greater indicates positive sensitization.[77,78] A positive control assay is typically performed with mitogenic phytohemagglutinin. For quality control, morphological analysis is often performed to confirm the presence of lymphoblasts in positive reactions and to exclude cytotoxicity in negative reactions.

An optimized, commercially available LTT test called Memory Lymphocyte Immunostimulation Assay (MELISA) was developed by Astra Pharmaceuticals (now AstraZeneca) in Södertälje,

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Sweden. It differs by the use of defibrinated blood instead of anticoagulant-treated blood, the cultivation of lymphocytes in cultures of 1×10^6 cells instead of 2×10^5 (macrocultures instead of microcultures), and a double reduction of adherent cells (monocytes/macrophages) at the start and at the end of cultivation. In addition, the use of inactivated human serum instead of fetal calf serum makes MELISA more sensitive by decreasing spontaneous proliferation in control cultures.[79]

As an in vitro method, LTTs offer unique benefits. Unlike patch testing, LTT cannot induce sensitization. It also has the ability to evaluate circulating lymphocytes in addition to those specifically targeted to the skin, enabling it to detect both dermally and non-dermally sensitized immune cells. Challenges for widespread use include cost, limited number of antigens that may be tested, and availability of specialized laboratories. Perhaps the most important limitation is the frequent lack of clinical correlation; acceptance by dermatologists is not widespread.

Only a handful of articles have been published with data on LTT testing for titanium allergy (Table 4).[47,59,61,62,76,77,80–84] Three studies by the same research group reported no positive results to titanium in any of 97 total patients, both with and without metal sensitivity. However, the authors disclosed that high-enough concentrations to activate the lymphocytes may not have been achieved because of solubility issues.[47,80,81] Most positive results reported utilized the MELISA technique.[59,61,76,77,79,83] There is a significantly greater prevalence of titanium hypersensitivity detected by MELISA than by patch testing, which is consistent with past reported investigations of other allergens; some authors attribute this to a greater sensitivity of this test for systemic reactions.[85,86] A recent prospective analysis assessing metal sensitivity in patients with THA reported 35% of their patients to be positive to titanium in LTT, all of whom patch tested negative.[62] Another study by Müller and Valentine-Thon[61] including 56 patients with various health problems after receiving titanium implants observed similar results; they found that 37.5% of their patients tested positive to titanium on LTT, all of whom patch tested negative as well. Removal of the implants resulted in dramatic improvement of clinical symptoms in 54 of the 56 patients (2 chose not to undergo the procedure). Interestingly, they also observed normalization of LTT response following implant removal.[61]

Other Tests

Other testing methods reported for metal hypersensitivity include lymphocyte migration inhibition,[87] intradermal testing,[88] BiDORT,[89,90] and a proposed triple assay consisting of (1) LTT, (2) cytokine analysis using enzyme-linked immunosorbent assay (ELISA), and (3) migration inhibition assay.[80] Yamauchi et al[91] reported a man with new-onset widespread nummular eczema and localized dermatitis overlying a newly implanted titanium-containing pacemaker who had negative patch tests to the pacemaker components including titanium; however, an intradermal test using the patient's serum, which had been incubated for a month with small titanium fragments, was positive. Sicilia et al[66] found that 7 of their 9 patients who were patch test positive to titanium also had type I hypersensitivity on prick testing.

Reported Adverse Reactions to Titanium

The first reported titanium hypersensitivity reactions to implants involved cardiac pacemakers in the 1980s. Over the years, additional cases of titanium hypersensitivity have been reported in other settings such as occupational inhalation, dental implants, osteosynthesis, joint replacements, surgical clips, jewelry, cranioplasty, Amplatz occluder, and suture anchors (Table 5).[70,75,89,90,92–109] A wide range of clinical manifestations have been reported, including local and/or generalized eczema, pruritus, pain, swelling, impaired fracture healing, DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, sterile necrosis, unexplained implant failure, and even death. In most cases, allergy testing was performed with varying and somewhat unreliable results. Diagnosis was largely confirmed by the absence of other potential allergenic triggers and/or absence of other positive diagnostic allergy testing, in conjunction with resolution of clinical symptoms once the titanium exposure was eliminated.

Pacemaker Case Reports

Our literature search found 9 reports of suspected sensitivity to titanium in pacemakers. Three reported positive patch tests to titanium; these 3 pacemakers were removed and replaced with pacemakers coated with silicone (unsuccessful),[94] parylene (unsuccessful),[75] and polytetrafluoroethylene (PTFE) (successful).[96] The outcome of 2 of the 9 cases were not reported.[90,91] One patient died,[92] 1 resolved within 4 weeks of implant removal,[93] 1 patient had spontaneous resolution without removal of the implant,[95] and another had successful replacement with a gold-coated pacemaker.[97]

Dental Implant Case Reports

Three cases of reactions to titanium-containing dental implants describe facial eczema,[100] gingival hyperplasia,[98] and pain/swelling/erythema with granulomatous reaction surrounding the implants.[99] Patch testing was not performed in these cases; 1 reported a positive LLT.[100] Two had complete resolution after removal of the implants[98,100]; follow-up was not reported in the other case.[99] Some dental experts believe that oral-implant–related titanium hypersensitivity is currently underreported because of failure to recognize it as a potential etiological factor[110] and that it should be taken into consideration with unexplained failure cases such as spontaneous rapid exfoliation of Ti implants,[111] and/or successive dental implant failures in some patients known as "cluster patients."[112,113]

Orthopedic Implant Case Reports

Three case reports of reactions to orthopedic devices have been reported. Thomas and colleagues[101] reported a patient with impaired fracture healing and local eczema over the site of a titanium-based osteosynthesis plate. Although patch testing to titanium was negative, the LTT was positive. After removal of the titanium plate, the dermatitis resolved, and the LTT returned to normal levels.[101]

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TABLE 4. Lymphocyte Transformation Testing for Titanium Hypersensitivity in Larger Series of Patients

Reference	No. Patients	No. Positive (%)	Comments
MELISA			
Stejskal,[79] 1997 (Sweden)	650 Patients with clinically verified or suspected MHS	19 (2.9)	All patients reported health problems following metallic dental restorations (Ti content not reported).
Stejskal et al,[76] 1999 (Sweden)	3162 Patients: 3046 with suspected MHS and 116 controls	184 (5.8)	All patients reported health problems after receiving various metallic implants (Ti content NR).
Valentine-Thon and Schiwara,[77] 2003 (Germany)	250 Patients with suspected metal allergy	105 (42)	All patients reported health problems after receiving various metallic implants (Ti content NR).
Müller and Valentine-Thon,[61] 2006 (Germany)	56 Patients who developed clinical symptoms after receiving a Ti implant	21 (37.5)	All patients reported health problems after receiving a Ti-based implant; 54 patch tested negative to Ti.
Valentine-Thon and Schiwara,[77] 2003 (Germany)	700 Patients with suspected MHS	29 (4.1)	All patients reported health problems after receiving various metallic implants (Ti content NR).
Frigero et al,[59] 2011 (Italy)	20 Of 100 patients included in the study were tested before, and one year after TKA or THA	0 (0)	Unclear if any of the 20 MELISA-tested patients had Ti implants.
200 ppb CpTi LTT			
Hallab et al,[80] 2000 (USA)	6 Patients: 3 patients with stable THAs and a history of MHS, and 3 control subjects without implants or history of MHS	0 (0)	Triple assay study. All hip implants contained Ti-6Al-4V alloy stems, cobalt-chrome alloy femoral heads, an ultrahigh molecular weight polyethylene acetabular liner in a Ti-6Al-4V alloy shell, and Ti-6Al-4V alloy bone screws.
0.001 mM Ti LTT			
Hallab et al,[47] 2004 (USA)	34 Patients: 7 with stable metal-on-polyethylene THAs, 9 with stable metal-on-metal THAs, 6 with OA and no history of MHS, and 12 control subjects without implants	0 (0)	Due to low solubility, higher concentrations of Ti were not studied. Ti content of implants NR.
Hallab et al,[81] 2005 (USA)	57 Patients: 17 patients with THA and no history of MHS, 18 patients with OA, and 22 control subjects without implants	0 (0)	Due to low solubility, higher Ti concentrations were not studied. Ti content of implants NR.
"ndard LTT Protocol"			
Vermes et al,[62] 2013 (Hungary)	40 Patients undergoing THA with no history of MHS	14 (35)	All hip implants contained Ti-6Al-4V alloy stems, Co-Cr femoral heads, and an ultrahigh molecular weight polyethylene acetabular liner in a Ti-6Al-4V alloy shell.
TiO_2 particles, 10^{-4} M and 10^{-5} M, and grade 4 CpTi disks with 3 different surface modifications submerged in cultures			
Thomas et al,[82] 2013 (Germany)	20 Patients: 14 controls and 6 patients with asymptomatic Ti dental implants	0 (0)	Researchers also measured various cytokine levels and reported reduced inflammatory cytokine response and concomitant IL-10 production of lymphocytes and monocytes in symptom-free Ti dental implant patients.

OA indicates osteoarthritis; MHS, metal hypersensitivity; NR, not reported; TiO_2, titanium dioxide.

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TABLE 5. Reports of Suspected Titanium Hypersensitivity Reactions

Reference, Type of Exposure	Type of Titanium	Clinical Presentation	Testing to Titanium	Outcome
Pacemaker				
Brun and Hunziker,[91] 1980	Ti, grade NR	Local eczema	Patch test: negative to Ti metal and $TiCl_4$	NR
Peters et al,[75] 1984	CpTi	Local swelling and pruritus × 4 implant attempts	Patch test: positive to Ti metal disk with artificial sweat	Device was replaced with a custom-made parylene coating, but was later removed due to a similar reaction.
Verbov,[92] 1985	Ti, grade NR	Aseptic purulent drainage × 4 implant attempts	Patch test: not performed	All implants failed and were removed. Patient died shortly after.
Buchet et al,[93] 1992	Not specified	Generalized nummular dermatitis	Patch test: not performed	Pruritus resolved within 5 d of removing the device; eczema cleared within 4 wk.
Abdallah et al,[94] 1994	Ti, grade NR	Skin vesicles and erosion; sterile serous fluid collections; 3 implant attempts	Patch test: positive for Ti and polyurethane; negative for Si and ethylenediamine (formulations NR)	Device was unsuccessfully replaced with a custom-made silicone coated device, which was later removed.
Viraben et al,[95] 1995	Ti, grade NR	Local eczema with granulomatous reaction	Patch test: negative to 1% TiO_2 and a square of metal pacemaker. Energy Dispersive Analysis X-ray (EDAX) detected presence of Ti particles in the granulomatous tissue	Spontaneous resolution
Yamauchi et al,[90] 2000	Ti, grade NR	Local eczema with subsequent generalized nummular dermatitis	Patch test: negative to implant metal, intracutaneous test: positive with patient's serum incubated with Ti pieces × 1 month, LTT: positive—subjected 10% of the incubated serum to a ^{3}H-thymadine incorporation test (SI = 2.35)	NR
Ishii et al,[96] 2006	CpTi	Local eczema, granulomatous reaction, and partial exposure of the device	Patch test: positive to Ti metal	Pacemaker was successfully reimplanted with a coat of PTFE.
Syburra et al,[97] 2010	Ti, grade NR	Sterile wound necrosis with 2 implant attempts	Patch test: negative to "manufacturer's specified patch test"; details of patch test formulation NR	Replaced successfully with gold coated pacemaker and polyethylene coated leads
Dental implants				
Mitchell et al,[98] 1990	CpTi	Persistent gingival hyperplasia	No testing performed	Complete resolution following replacement of the Ti implants with custom-fabricated gold implants
du Preez et al,[99] 2007	CpTi	Pain, swelling, and erythema with granulomatous reaction	No testing performed	Implants removed; follow-up NR
Egusa et al,[100] 2008	CpTi	Facial eczema	Patch test: patient declined patch testing, LLT: positive to 4% $TiCl_3$ with SI = 2.39	Implants removed with complete resolution of symptoms

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TABLE 5. ***(Continued)***

Reference, Type of Exposure	Type of Titanium	Clinical Presentation	Testing to Titanium	Outcome
Orthopedic				
Thomas et al,[101] 2006, Osteosynthesis	CpTi	Local eczema, impaired fracture healing	Patch test: negative to TiO_2 (formulation NR); LTT: positive to 8 μg/mL TiO_2 (SI = 3.35) and 0.8 μg/mL TiO_2 (SI = 3.16)	After removal of titanium material, eczema cleared, fracture healed, LTT levels normalized.
Opstal and Verheyden,[102] 2011, TKA	Ti-6Al-4V alloy	Pain, swelling and dermatitis at surgical site; aseptic loosening of the implant	Patch test: negative to Ti (formulation NR)	Complete resolution after 2nd revision with custom oxinium (oxidized zirconium)
Goto et al,[103] 2013, rotator cuff suture anchors	Ti-Al-V alloy	Erythema and itching of face, trunk and hands	Patch test: negative to Ti (formulation NR)	Complete resolution after removal
Neurosurgical Implants				
Nawaz and Wall,[104] 2007, spinal bioprosthesis	Ti-6Al-4V alloy	DRESS syndrome	Patch test: positive to Ti and Ni (formulation NR)	Implant not removed due to extensive fibrosis. Slow oral corticosteroid taper over 6 mo
Hettige and Norris,[105] 2012, cranioplasty	Ti, grade NR	Mortality due to diffuse brain swelling	Patch test: not performed Postmortem blood test: "elevated levels of mast cell tryptase, which confirmed the examiner's suspicion…, that an immunological response to titanium had occurred."	Extensive postmortem investigation revealed no other cause of mastocytosis or other cause of death
Other				
Redline et al,[106] 1986, occupational inhalation of metallic fumes and dust	Retrieved particulates consisted of Al, Ti, Zi, Ni, Al silicates and silica	Granulomatous pulmonary disease	Patch test: not performed, LTT: positive to 10 μg/mL $TiCl_4$ (SI = 2.1) while on 10 mg daily prednisone; negative to other particles	NR
Tamai et al,[89] 2001, surgical clips	Ti, NR	Exacerbation of atopic dermatitis	Patch testing: not performed, LTT: not performed, BiDORT: positive to Ti and TiO_2	Clips removed, atopic dermatitis not completely resolved at 12 mo
High et al,[107] 2006, ear piercing	Ti-Al-V alloy	Nodular granulomatous reaction	Patch testing: not performed (patient declined)	Granulomatous tissue containing Ti particles years later was excised without recurrence
Belohlavek and Belohlavkova,[108] 2013 Amplatzer occluder	NITINOL	Generalized pruritic exanthema	Patch test: not performed, MELISA: strongly positive to $TiCl_3$ (30.9) and TiO_2 (11.2), and mildly positive to Ni (3.5)	Three days after removal, skin lesions resolved.
Bernard et al,[70] 2013 (Belgium)	TiN 5% pet and, C_4O_8Ti 5% pet	Atopic 8-y-old girl with a history of severe Cr MHS experienced MHS reactions to 2 Ti allergen formulations	Patch testing: positive to TiN 5% pet and C_4O_8Ti 5% pet; Negative to Ti 10% pet, TiO_2 10% pet, and $CaTiO_3$ 10% pet	Chromium was detected in the commercial Ti allergens (0.21-10.82 ppm), raising concern for the role of impurities in Ti patch testing.

NR indicates not reported; $TiCl_4$, titanium chloride; TiN, titanium nitride; C_4O_8Ti, titanium oxalate; MHS, metal hypersensitivity; TiO_2, titanium dioxide; $CaTiO_3$, calcium titinate.

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Opstal and Verheyden[102] reported a patient with pain, swelling, dermatitis, and double implant failure of a TKA composed of separate oxinium and titanium components. Although patch testing to titanium was negative, both implant failures were found to be due to aseptic loosening of the titanium component exclusively, as seen on imaging and at 2 revision surgeries. After replacing the titanium with a custom oxinium counterpart, clinical symptoms resolved, and the new implant did not loosen.[102] The third case, reported by Goto et al,[103] described a patient with erythema and itching of the face, trunk, and hands who had negative patch tests to metal components but whose symptoms resolved after removal of rotator cuff suture anchors composed of a titanium alloy.

Neurosurgical Implant Case Reports

Two serious reactions have been alleged to be due to titanium hypersensitivity in neurosurgical implants. Nawaz et al[104] described a previously healthy 19-year-old man, who had DRESS syndrome with interstitial nephritis after acquiring a Ti6Al4V spinal bioprosthesis. Association with the titanium implant was suspected, and patch testing revealed a "strongly positive" reaction to titanium and nickel. Extensive fibrosis precluded removal of the implant, and the patient was medically managed with a slow oral corticosteroid taper over 6 months. Hettige and Norris[105] reported a 64-year-old woman with a history of nickel allergy who died of diffuse brain swelling after undergoing cranioplasty with a titanium skull plate. Postmortem examination revealed high blood levels of mast cell tryptase, suggesting a massive immune reaction with no other source identified.

Cardiovascular Implant Case Reports

Belohlavek et al[108] reported a 40-year-old woman with patent foramen ovale requiring a nitinol Amplatz occluder, who subsequently developed a generalized exanthema, as well as a reported increased sensitivity (contact dermatitis) to titanium earrings and a new oral burning sensation after consumption of certain foods. MELISA testing was strongly positive to titanium trichloride (30.9) and titanium dioxide (11.2) and mildly positive to nickel (3.5). Her symptoms were so debilitating, removal of the implant was performed, requiring an open-heart procedure. Three days after removal, her clinical symptoms resolved.[108]

Pulmonary Disease

A case of granulomatous pulmonary disease with associated pulmonary deposition of titanium was reported in a 45-year-old man who worked as a furnace feeder for an aluminum smelting company; his job involved chronic exposure to various metallic fumes and dusts. Lymphocyte transformation testing was positive to titanium, but not to any other metal particulates retrieved from his lung tissue. The researchers also demonstrated negative LTT results in 3 occupational painters as control subjects, who were also chronically exposed to titanium-based paint fumes, but who had no observed pulmonary hypersensitivity reactions.[106] Pulmonary alveolar proteinosis causing lung tissue damage has also been reported because of chronic inhalation of titanium particles from paint fumes.[114,115] Although it is notable that the cause was attributed to titanium, the pathogenesis of pulmonary alveolar proteinosis is still unknown and therefore will not be further discussed under the umbrella of type IV hypersensitivity reactions.

Titanium in Personal Care Products

A comprehensive literature search found no reported cases of hypersensitivity to titanium in personal care products such as sunscreen and cosmetics. However, a case report of a woman with a history of atopic dermatitis and breast cancer, who had a hypersensitivity reaction to her titanium surgical clips, subsequently reported increased sensitivity to cosmetics with high titanium dioxide content.[89]

Differential Diagnoses

Sensitivity to other metals or materials may masquerade as titanium sensitivity (Table 6).[116–122] A report of pacemaker dermatitis in 1980 revealed that the stainless-steel screws in the device were inciting contact allergy to nickel, chromium, and cobalt, but not to titanium.[115] Another case of pacemaker dermatitis initially thought to be due to titanium was found to be due to epoxy resin.[116] More recently, 2 cases of contact dermatitis due to titanium spectacle frames reportedly determined that the actual allergens were nickel and/or palladium present in the "titanium" material.[117,118] An informative case of impaired wound healing following osteosynthesis discovered that the causative allergen was actually a significant amount of nickel in the "commercially pure" titanium devices used.[119] A case of allergic contact stomatitis was determined to be due to the titanium-nitride coating on dental implant abutments and completely resolved once the implants were replaced with CpTi abutments.[120] A more straightforward case of severe contact dermatitis due to a titanium alloy (Ti-6Al-4V) halo fixation pins reported clearly positive patch test results to vanadium (a major component of the alloy).[121]

Management

The criterion standard for managing type IV hypersensitivity is avoidance of the responsible allergen. If a patient with a titanium implant presents with significant clinical symptoms strongly suggestive of titanium hypersensitivity, removal of the implant, if possible, may be considered. However, many titanium implants are intended to function for the remaining lifetime of the patient, and removal of the device may result in significant morbidity, loss of essential function, or even mortality. In these clinical scenarios, risks and benefits will need to be carefully weighed. Titanium is currently considered to be the most biocompatible metal and is often reserved as a last resort for implants in patients with metal hypersensitivity.

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TABLE 6. Case Reports of Suspected Titanium Allergy Found to be Due to Other Allergens

Reference	Type of Ti	Clinical Presentation	Testing Performed	Outcome
Pacemaker				
Tilsley and Rotstein,[115] 1980	Titanium, grade NR, stainless-steel screws	Lichenified, dusky, red slightly indurated plaques with eczematous changes on arms and legs	Patch test: negative to Ti; positive to Ni, Co, and CrO_4 (formulations NR)	NR
Romaguera and Grimalt,[116] 1981	Titanium, grade NR	Local eczema	Patch test: negative to Ti metal, TiO_2 1%, and $TiCl_4$ 0.1% and 0.01%; strongly positive to epoxy resin 1%	NR
Spectacle frames				
Suhonen and Kanerva,[117] 2001	99.7% pure titanium with gold plating (90% gold, 7% palladium, 3% copper)	Dermatitis at contact sites with spectacle frames	Patch test: not performed to Ti; positive to Cl_2Pd 2% and $AuNaO_3S_2$ 0.5%	NR
Bircher and Stern,[118] 2001	"Titanium" frames found to be composed of gold-plated nickel-palladium alloy with trace titanium and cobalt	"Dermatitis" at contact sites with spectacle frames	Patch test: negative to CpTi metal plate and TiO_2 1%; positive to Ni, Co, Pd (formulations NR) and to a piece of the frame	NR
Other				
Thomas et al,[119] 2011, osteosynthesis	"Commercially pure titanium" found to have significant amounts of nickel in eluate	Impaired wound healing, local eczema	Patch test: negative to TiO_2; positive to Ni and Co (formulation NR), LTT: negative to TiO_2 10^{-4} M and 10^{-5} M, and $CoCl_2$ 10^{-4} M, 10^{-5} M, and 10^{-6} M; positive to $NiSO_4$ 10^{-4} M, 10^{-5} M, and 10^{-6} M (SI = 14.95)	Eczema resolved after removal
Lim et al,[120] 2012, dental implants	CpTi with TiN-coated abutments	Pain and erythema of gingiva in contact with abutments	Patch test: not performed with CpTi; positive to TiN-coated CpTi specimens; negative to TiN powder (formulation NR)	Symptom resolution after implants replaced with custom uncoated Ti
Coulter et al,[121] 2012, halo fixation pins	Titanium alloy (Ti-6Al-4V)	Bilateral periorbital edema, progressive facial swelling, and dermatitis surrounding halo pin sites	Patch test: negative to Ti and positive to V (formulations NR)	Resolution after removal of pins with complete bony healing at 3 mo

CrO_4 indicates chromate; TiO_2, titanium dioxide; $TiCl_4$, titanium chloride; Cl_2Pd, palladium chloride; $AuNaO_3S_2$, gold sodium thiosulfate; $CoCl_2$, cobalt chloride; $NiSO_4$, nickel sulfate; TiN, titanium nitride.

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Zirconium, gold, and oxinium replacements may be considered. Oliva and colleagues reported a patient with amelogenesis imperfecta, who required full-mouth dental implants; titanium (and other metal sensitivity) was diagnosed based on elevated MELISA levels. Zirconium oxide implants and restorations were utilized with no complications at a 3-year follow-up.[123] Custom-fabricated gold dental implants resulted in resolution of persistent gingival hyperplasia after replacing a prior titanium implant.[98] Oxinium has successfully replaced titanium in a case of TKA with aseptic loosening, as described previously.[102] Successful replacement of pacemakers with gold-coated devices,[97] as well as wrapping with PTFE sheets,[96] has been described in cases of titanium pacemaker dermatitis.

Medical management has also been reported. After 3 unsuccessful pacemaker implant attempts in a 10-year-old girl because of titanium hypersensitivity (including a failed attempt at coating the pacemaker case with silicone), the patient was managed medically with oral atropine sulfate every 6 hours with adequate control.[94] Authors of the titanium implant–induced DRESS syndrome case reported successful medical management with 6-month taper of oral corticosteroids, after determining that the implant could not be surgically removed because of extensive fibrosis.[104]

Various techniques in tissue engineering to replace cartilage may someday be a valid alternative to joint arthroplasty in patients with degenerative joint disease—with or without metal hypersensitivity—but research is still in its infancy. Success of stem cell therapy for osteochondral defects in animals in vivo is well established, although there is currently only a small body of evidence in human subjects.[124] The procedure involves taking autologous bone marrow–derived mesenchymal stem cells from the iliac crest and implanting them into the diseased articular space in an effort to heal cartilage or joint pathology. A review of 844 mesenchymal stem cell implant procedures and reported adverse events concluded that the procedure appears to be safe.[125] Multiple research groups are currently recruiting patients for larger clinical trials.[126]

Controversy Regarding Metal Sensitivity Testing for Implants

In general, diagnostic evaluation for allergy to implanted metallic devices is controversial. It is unresolved whether a cutaneous type IV hypersensitivity reaction has any clinical correlation with a peri-implant hypersensitivity reaction, as antigen-presenting cells in the skin (dendritic cells) differ from those in deeper tissues. Thyssen et al[127] demonstrated that the overall risk of developing extracutaneous allergic reactions following THA is comparable in metal patch test–positive and patch test–negative subjects. Swiontkowski et al[128] showed that the conversion from negative to positive metal patch test reactivity (chromium, nickel, and cobalt) in 242 patients before and after stainless-steel implant surgery was similar to the rate of conversion of positive to negative patch tests; in that study, patch tests were read at 48 hours only and, for the postsurgery tests, were read by the patient.

With lack of an evidence-based approach, expert opinions are sought as to when, how, and on whom patch testing should be performed. There are heterogeneous attitudes in the dermatological community regarding preimplantation evaluation for metallic devices. Most agree that individuals without a reported history of metal hypersensitivity reactions need not be screened prior to device implantation.[129] A survey conducted at the European Society of Contact Dermatitis and American Contact Dermatitis Society meetings revealed that of 119 respondents, 54% of patch-testing dermatologists believe that a patient with suspected moderate to severe metal dermatitis should undergo patch testing and/or LTT before implantation of a metallic device.[130] Thirty-eight percent agreed with a German consensus panel of dermatologists, allergists, and orthopedic surgeons that it is adequate to counsel the patient and surgeon to just use a titanium device in anyone with a history of metal allergy.[131]

If metal hypersensitivity to implanted metals occurs, it is unclear whether metal hypersensitivity induces implant failure or implant failure results in metal hypersensitivity. A Delphi consensus study among orthopedic arthroplasty surgeons in the United Kingdom concluded not only that routine metal allergy screening prior to joint arthroplasty is not essential, but also that the use of traditional cobalt chromium/stainless-steel implants is recommended regardless of the patient's metal allergy status.[132] Although most patients with a preexisting metal allergy will do well despite implant allergen exposure, completely ignoring history of prior metal allergy could expose a small number of patients to the potential morbidity of a failed device as well as increased costs in further management. In some cases, disregarding a history of known allergies in a patient who subsequently develops complications could lead to legal actions against treating physicians, especially in the United States. Recent reviews have proposed a pragmatic approach, as well as a diagnostic algorithm to guide clinical workup of metallic implant patients with putative metal hypersensitivity, both before and after implantation.[133,134]

Preimplant Testing

The approach to a patient with a history of metal allergy, who is considering implantation of a titanium device, should begin with a thorough history. Although immune response to an implant remains unpredictable, patients with a reported history of sensitivity to a metallic device or metal jewelry may be more likely to have an immune response to an implant.[17] Prior reactivity to "titanium" jewelry or eyeglass frames is not a reliable source of titanium exposure. If a patient reports a previous hypersensitivity reaction to an implanted "titanium" device (eg, plates, screws), it is important to determine the specific alloy, remembering that even commercially pure-grade titanium implants could potentially contain ulterior metal impurities.[5,119] A MELISA assay will be normal after avoidance of the offending metal.[61,101,134] Similarly, lymphocyte reactivity would also be normal preceding implantation of a potential metal allergen and therefore would not serve as a legitimate screening tool. For patients who are planning to receive an implant intended to remain for the rest of their life, and whose removal would be impossible or pose extremely high risk, some type of

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screening is direly needed. Temporarily implanting an easily retrievable sample of the proposed titanium device may provide guidance, although would not account for mechanical corrosion.

DISCUSSION

Life expectancy is increasing. Inevitably, this demographic change will result in increased use of metallic implant devices. Titanium sensitivity will likely continue to be considered in cases of failed devices, unexplained symptoms, and skin reactions. It is unclear whether prior metal sensitivity can cause implant failure, or implant failure can induce metal sensitivity. In the case of titanium hypersensitivity, it is highly unlikely that patients with only prior cutaneous exposure to titanium are sensitized, given that titanium in its most common form (TiO_2) does not penetrate the epidermis. Like all metals, titanium is not completely inert; biocorrosion may occur with titanium implants and, with it, the potential to elicit an immune reaction. Researchers have reported a higher prevalence of titanium hypersensitivity among patients sensitive to other metals.[7,62,76] Could a type IV hypersensitivity response to alloy components (such as nickel or cobalt) recruit cells to elicit an immune response to titanium, similar to the coreactions commonly seen with neomycin and bacitracin? Or are patients with titanium sensitivity genetically more prone to be sensitive to all metals? Or do the reported cases of titanium sensitivity simply represent T cell reactivity with no clinical relevance? Complete elucidation of titanium hypersensitivity and its relevance to implant failure will require intensive prospective studies that have not been performed to date, in large part because no standardized diagnostic test exists.

CONCLUSIONS

Titanium allergy appears to be exceptionally rare. In cases of suspected titanium sensitivity, it is prudent to first look for other potential causes such as reactions to alloy components or other metal impurities, particularly nickel. Patch testing is unreliable because of the lack of penetration of titanium salts through the epidermis. Lymphocyte proliferation assays are not widely accepted. The definitive treatment for confirmed titanium hypersensitivity reaction is removal of the device; however, medical management is possible in some cases. There still remains no useful screening tool to predict a potential hypersensitivity reaction to implanted titanium devices, and further investigation is needed.

REFERENCES

1. Oshida Y. Introduction. In: Oshida Y, ed. *Bioscience and Bioengineering of Titanium Materials*. 2nd ed. Oxford, UK: Elsevier Science Ltd; 2013:1–8.
2. Standard specification for titanium and titanium alloy strip, sheet, and plate [ASTM Web site]. 1996–2014. Available at: http://www.astm.org/Standards/B265.htm. Accessed August 7, 2014.
3. Donachie MJ Jr. The titanium alloys. In: Donachie MJ Jr. *Titanium: A Technical Guide*. 2nd ed. Materials Park, OH: ASM International; 1988:5–11.
4. Oshida Y. Materials classification. In: Oshida Y, ed. *Bioscience and Bioengineering of Titanium Materials*. 2nd ed. Oxford, UK: Elsevier Science Ltd; 2013:9–34.
5. Harloff T, Hönle W, Holzwarth U, et al. Titanium allergy or not? "Impurity" of titanium implant materials. *Health* 2010;2(4):306–310.
6. Vijayaraghavan V, Sabane AV, Tejas K. Hypersensitivity to titanium: a less explored area of research. *J Indian Prosthodont Soc* 2012;12(4):201–207.
7. Hallab N. Metal sensitivity in patients with orthopedic implants. *J Clin Rheumatol* 2001;7(4):215–218.
8. Granchi D, Cenni E, Trisolino G, et al. Sensitivity to implant materials in patients undergoing total hip replacement. *J Biomed Mater Res Part B: Appl Biomater* 2006;77B:257–264.
9. Warshaw EM, Belsito DV, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. *Dermatitis* 2013;24:50–59.
10. Schäfer T, Bohler E, Ruhdorfer S, et al. Epidemiology of contact allergy in adults. *Allergy* 2001;56:1192–1196.
11. Warshaw EM, Kingsley-Loso JL, DeKoven JG, et al. Body piercing and metal allergic contact sensitivity: North American Contact Dermatitis Group Data, 2007 to 2010. *Dermatitis*. 2014;25:255–264.
12. Holgers KM, Roupe G, Tjellstrom A, et al. Clinical, immunological and bacteriological evaluation of adverse reactions to skin-penetrating titanium implants in the head and neck region. *Contact Dermatitis* 1992;27:1–7.
13. Hallab NJ, Caicedo M, Finnegan A, et al. T_H1 type lymphocyte reactivity to metals in patients with total hip arthroplasty. *J Orthop Surg* 2008;3:6.
14. Thomas P, Summer B, Sander CA, et al. Intolerance of osteosynthesis material: evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and T_H1-type cytokine expression in the peri-implantar tissue. *Allergy* 2000;55:969–972.
15. Summer B, Paul C, Mazoochian F, et al. Nickel (Ni) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni. *Contact Dermatitis*. 2010;63:15–22.
16. Aquino M, Mucci T. Systemic contact dermatitis and allergy to biomedical devices. *Curr Allergy Asthma Rep* 2013;13:518–527.
17. Basko-Plluska JL, Thyssen JP, Schalock PC. Cutaneous and systemic hypersensitivity reactions to metallic implants. *Dermatitis* 2011;22(2):65–79.
18. Merritt K, Rodrigo JJ. Immune response to synthetic materials: sensitization of patients receiving orthopaedic implants. *Clin Orthop Relat Res*. 1996;326:71–79.
19. Sadrieh N, Wokovich AM, Gopee NV, et al. Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO_2 particles. *Toxicol Sci* 2010;115(1):156–166.
20. Pinheiro T, Pallon J, Alves LC, et al. The influence of corneocyte structure on the interpretation of permeation profiles of nanoparticles across skin. *Nucl Instr Meth Phys Res B* 2007;260(1):119–123.
21. Cadosch D, Chan E, Gautschi OP, et al. Metal is not inert: role of metal ions released by biocorrosion in aseptic loosening—current concepts. *J Biomed Mater Res* 2009;91A:1252–1262.
22. Bozinni B, Carlino P, Urzo LD, et al. An electrochemical impedance investigation of the behavior of anodically oxidized titanium in human plasma and cognate fluids, relevant to dental applications. *J Mater Sci Mater Med* 2008;19:3443–3453.
23. Martin SF. T lymphocyte-mediated immune responses to chemical haptens and metal ions: implications for allergic and autoimmune disease. *Int Arch Allergy Immunol* 2004;134:186–198.

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24. Messori L, Orioli P, Banholzer V, et al. Formation of titanium(IV)-transferrin by reaction of human serum apotransferrin with titanium complexes. *FEBS Lett* 1999;442:157–161.
25. Tinoco AD, Eames EV, Valentine AM. Reconsideration of serum Ti(IV) transport: albumin and transferrin trafficking of Ti(IV) and its complexes. *J Am Chem Soc* 2008;130:2262–2270.
26. Urban RM, Jacobs JJ, Tomlinson MJ, et al. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J Bone Joint Surg Am* 2000;82:457–476.
27. Lalor PA, Revell PA, Gray AB, et al. Sensitivity to titanium: a cause of implant failure? *J Bone Joint Surg Br* 1991;73B:25–28.
28. Hedenborg M. Titanium dioxide induced chemiluminescence of human polymorphonuclear leukocytes. *Int Arch Occup Environ Health* 1988; 61(1–2):1–6.
29. Kumazawa R, Watari F, Takashi N, et al. Effects of Ti ions and particles on neutrophil function and morphology. *Biomaterials* 2002;23:3757–3764.
30. Voggenreiter G, Leithing S, Brauer H, et al. Immuno-inflammatory tissue reaction to stainless-steel and titanium plates used for internal fixation of long bones. *Biomaterials* 2003;24:247–254.
31. Bi Y, Van De Motter RR, Ragab AA, et al. Titanium particles stimulate bone resorption by inducing differentiation of murine osteoclasts. *J Bone Joint Surg Am* 2001;83:501–508.
32. Cadosch D, Chan E, Gautschi OP, et al. Titanium IV ions induced human osteoclast differentiation and enhanced bone resorption in vitro. *J Biomed Mater Res A* 2009;91:29–36.
33. Katou F, Andoh N, Motegi K, et al. Immuno-inflammatory responses in the tissue adjacent to titanium miniplates used in the treatment of mandibular fractures. *J Craniomaxillofac Surg* 1996;24(3):155–162.
34. Frisken KW, Dandie GW, Lugowski S, et al. A study of titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep. *Aust Dent J* 2002;47(3):214–217.
35. Schliephake H, Lehmann H, Kunz U, et al. Ultrastructural findings in soft tissues adjacent to titanium plates used in jaw fracture treatment. *Int J Oral Maxollofac Surg* 1993;22:20–25.
36. Thewes M, Kretschmer R, Gfesser M, et al. Immunohistochemical characterization of the perivascular infiltrate cells in tissues adjacent to stainless steel implants compared with titanium implants. *Arch Orthop Trauma Surg* 2001;121:223–226.
37. Scales JT. Black staining around titanium alloy prostheses—an orthopaedic enigma. *J Bone Joint Surg Br* 1991;73(4):534–536.
38. Witt JD, Swann M. Metal wear and tissue response in failed titanium alloy total hip replacements. *J Bone Joint Surg Br* 1991;73:559–563
39. Konttinen YT, Zhao D, Beklen A, et al. The microenvironment around total hip replacement prostheses. *Clinical Orthopaedic Related Research* 2005;430:28–38.
40. Onodera K, Ooya K, Kawamura H. Titanium lymph node pigmentation in the reconstruction plate system of a mandibular bone defect. *Oral Surg Oral Med Oral Pathol* 1993;75:495–497.
41. Weingart D, Steinemann S, Schilli W, et al. Titanium deposition in regional lymph nodes after insertion of titanium screw implants in maxillofacial region. *Int J Oral Maxillofac Surg* 1994;23:450–452.
42. Foran JRH. Joint replacement [AAOS Web site]. 1995–2014. Available at: http://orthoinfo.aaos.org/menus/arthroplasty.cfm. Accessed July 27, 2014.
43. Bilhan H, Bilgin T, Cakir AF, et al. The effect of mucine, IgA, urea, and lysozyme on the corrosion behavior of various non-precious dental alloys and pure titanium in artificial saliva. *J Biomater Appl* 2007; 22:197–221.
44. Jacobs JJ, Silverton C, Hallab NJ, et al. Metal release and excretion from cementless titanium alloy total knee replacements. *Clin Orthop Relat Res* 1999;(358):173–180.
45. Jacobs JJ, Skipor MS, Black J, et al. Release and excretion of metal in patients who have a total hip-replacement component made of titanium-base alloy. *J Bone Joint Surg* 1991;73-A(10):1475–1486.
46. Leopold SS, Berger RA, Patterson L, et al. Serum titanium level for diagnosis of a failed, metal-backed patellar component. *J Arthroplasty* 2000;15:938–943.
47. Hallab NJ, Anderson S, Caicedo M, et al. Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty. *J Arthroplasty* 2004;19:88–93.
48. Schalock PC, Dunnick CA, Nedorost S, et al. American Contact Dermatitis Society core allergen series. *Dermatitis* 2013;24(1):7–9.
49. Uter W, Aberer W, Armario-Hita JC, et al. Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007–2008. *Contact Dermatitis* 2012;67(1):9–19.
50. Honari G, Ellis SG, Wilkoff BL, et al. Hypersensitivity reactions associated with endovascular devices. *Contact Dermatitis* 2008;59:7–22.
51. Reed KB, Davis MD, Nakamura K, et al. Retrospective evaluation of patch testing before or after metal device implantation. *Arch Dermatol* 2008; 144(8):999–1007.
52. Davis MDP, Wang MZ, Yiannias JA, et al. Patch testing with a large series of metal allergens: findings from more than 1,000 patients in one decade at Mayo Clinic. *Dermatitis* 2011;22(5):256–271.
53. Lhotka CG, Szekeres T, Fritzer-Szekeres M, et al. Are allergic reactions to skin clips associated with delayed wound healing? *Am J Surg* 1998; 176(4):320–323.
54. IIjima R, Ikari Y, Amiya E, et al. The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol* 2005;104:319–325.
55. Okamura T, Morimoto M, Fukushima D, et al. A skin patch test for the diagnosis of titanium allergy. *J Dent Res* 1999;78(5):1135.
56. Cancilleri F, DeGiorgis P, Verdoia C, et al. Allergy to components of total hip arthroplasty before and after surgery. *Ital J Orthop Traumatol* 1992; 18(3):407–410.
57. Granchi D, Cenni E, Tigani D. Sensitivity to implant materials in patients with total knee arthroplasties. *Biomaterials* 2008;29:1494–1500.
58. Waterman AH, Schrik JJ. Allergy in hip arthroplasty. *Contact Dermatitis* 1985;13:294–301.
59. Frigero E, Pigatto PD, Guzzi G, et al. Metal sensitivity in patients with orthopaedic implants: a prospective study. *Contact Dermatitis* 2011; 64:273–279.
60. Kręcisz B, Kieć-Świerczyńska M, Chomiczewska-Skóra D. Allergy to orthopedic metal implants-prospective study. *Int J Occup Med Environ Health* 2012;25(4):463–469.
61. Müller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence. *Neuroendocrinol Lett* 2006;27(suppl 1):31–35.
62. Vermes C, Kuzsner J, Bárdos T, et al. Prospective analysis of human leukocyte functional tests reveals metal sensitivity in patients with hip implant. *J Orthop Surg and Res* 2013;8:12.
63. Elves MW, Wilson JN, Scales JT, et al. Incidence of metal sensitivity in patients with total joint replacements. *Br Med J* 1975;4:376–378.
64. Milavec-Puretić V, Orlić D, Marusić A. Sensitivity to metals in 40 patients with failed hip endoprosthesis. *Arch Orthop Trauma Surg* 1998;117(6–7):383–386.
65. Menezes LM, Campos LC, Quintão CC, et al. Hypersensitivity to metals in orthodontics. *Am J Orthod Dentofacial Orthop* 2004;126(1):58–64.
66. Sicilia A, Cuesta S, Coma G, et al. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin Oral Implants Res* 2008;19(8):823–835.

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67. Basketter DA, Whittle E, Monk B. Possible allergy to complex titanium salt. *Contact Dermatitis* 2000:310–311.
68. Thomas P, Braathen LR, Dörig M. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy* 2009;64(8):1157–1165.
69. Newman MD, Stotland M, Ellis JI. Safety of nanosized particles in titanium dioxide– and zinc oxide–based sunscreens. *J Am Acad Dermatol* 2009;61:685–692.
70. Bernard S, Baeck M, Tennstedt D, et al. Chromate or titanium allergy—the role of impurities? *Contact Dermatitis* 2013;68(3):191–192.
71. Keane FM, Morris SD, Smith HR, et al. Allergy in coronary in-stent restenosis. *Lancet* 2001;357:1205–1206.
72. Paulsen SM, Nanney LB, Lynch JB. Titanium tetrachloride: an unusual agent with the potential to create severe burns. *J Burn Care Rehabil* 1998;19:377–381.
73. Lawson JJ. The toxicity of titanium tetrachloride. *J Occup Med* 1961;3:7–12.
74. Chitkara DK, McNeela BJ. Titanium tetrachloride burns to the eye. *Br J Ophthalmol* 1992;76:380–382.
75. Peters MS, Schroeter AL, van Hale HM, et al. Pacemaker contact sensitivity. *Contact Dermatitis* 1984;11:214–218.
76. Stejskal V, Danersund A, Lindvall A, et al. Metal-specific lymphocytes: biomarkers of sensitivity in man. *Neuroendocrinol Lett* 1999;20:289–298.
77. Valentine-Thon E, Schiwara H-W. Validity of MELISA® for metal sensitivity testing. *Neuroendocrinol Lett* 2003;24(1/2):57–64.
78. Stejskal VDM, Cederbrant K, Lindvall A, et al. MELISA—an in vitro tool for the study of metal allergy. *Toxicol In Vitro* 1994;8:991–1000.
79. Stejskal V. Human hapten-specific lymphocytes: biomarkers of allergy in man. *Drug Inform J* 1997;31:1379–1382.
80. Valentine-Thon E, Müller K, Guzzi G, et al. LTT-MELISA® is clinically relevant for detecting and monitoring metal sensitivity. *Neuroendocrinol Lett* 2006;27(suppl 1):17–24.
81. Hallab NJ, Mikecz K, Joshua JJ. A triple assay technique for the evaluation of metal-induced delayed-type hypersensitivity responses in patients with or receiving total joint arthroplasty. *Biomed Mater Res* 2000; (Appl Biometer)53:480–489.
82. Hallab NJ, Anderson S, Stafford T, et al. Lymphocyte responses in patients with total hip arthroplasty. *J Orthop Res* 2005;23:384–391.
83. Thomas P, Iglhaut G, Wollenberg A, et al. Allergy or tolerance: reduced inflammatory cytokine response and concomitant IL-10 production of lymphocytes and monocytes in symptom-free titanium dental implant patients. *BioMed Res Int* 2013;2013:539834
84. Carando S, Cannas M, Rossi P, et al. The lymphocytic transformation test (L.T.T.) in the evaluation of intolerance in prosthetic implants. *Ital J Orthop Traumatol* 1985;11:475–481.
85. Cederbrant K, Hultman P, Marcusson JA, et al. In vitro lymphocyte proliferation as compared to patch test using gold, palladium and nickel. *Int Arch Allergy Immunol* 1997;112:212–217.
86. Merritt K, Brown SA. Metal sensitivity reactions to orthopedic implants. *Int J Dermatol Mar* 1981;20(2):89–94.
87. Herbst RA, Lauerma AI, Maibach HI. Intradermal testing in the diagnosis of allergic contact dermatitis: a reappraisal. *Contact Dermatitis* 1993; 29:1–5.
88. Omura Y. New simple early diagnostic methods using Omura's "bi-digital O-ring dysfunction localization method" and acupuncture organ representation points, and their applications to the "drug & food compatibility test" for individual organs and to auricular diagnosis of internal organs-part I. *Acupunct Electrother Res* 1981;6:239–254.
89. Tamai K, Mitsumori M, Fujishiro S, et al. A case of allergic reaction to surgical metal clips inserted for postoperative boost irradiation in a patient undergoing breast-conserving therapy. *Breast Cancer* 2001; 8(1):90–92.
90. Yamauchi R, Morita A, Tsuji T. Pacemaker dermatitis from titanium. *Contact Dermatitis* 2000;42:52–53.
91. Brun R, Hunziker N. Pacemaker dermatitis. *Contact Dermatitis* 1980; 6(3):212–213.
92. Verbov J. Pacemaker contact sensitivity. *Contact Dermatitis* 1985; 12(3):173.
93. Buchet S, Blanc D, Humbert P, et al. Pacemaker dermatitis. *Contact Dermatitis* 1992;26(1):46–47.
94. Abdallah HI, Balsara RK, O'Riordan AC. Pacemaker contact sensitivity: clinical recognition and management. *Ann Thorac Surg* 1994;57(4): 1017–1018.
95. Viraben R, Boulinquez S, Alba C. Granulomatous dermatitis after implantation of a titanium-containing pacemaker. *Contact Dermatitis* 1995;33(6):437.
96. Ishii K, Kodani E, Miyamoto S, et al. Pacemaker contact dermatitis: the effective use of a polytetrafluoroethylene sheet. *Pacing Clin Electrophysiol* 2006;29:1299–1302.
97. Syburra T, Schurr U, Rahn M, et al. Gold-coated pacemaker implantation after allergic reactions to pacemaker compounds. *Europace* 2010;12(5): 749–750.
98. Mitchell DL, Synnott SA, VanDercreek JA. Tissue reaction involving an intraoral skin graft and CP titanium abutments: a clinical report. *Int J Oral Maxillofac Implants* 1990;5(1):79–84.
99. du Preez LA, Bütow KW, Swart TJP. Implant failure due to titanium hypersensitivity/allergy? Report of a case. *SADJ* 2007;62(1):22–25.
100. Egusa H, Ko N, Shimazu T, et al. Suspected association of an allergic reaction with titanium dental implants: a clinical report. *J Prosthet Dent* 2008;100(5):344–347.
101. Thomas P, Bandl WD, Maier S, et al. Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: case report and review of the literature. *Contact Dermatitis* 2006;55:199–202.
102. Opstal NV, Verheyden F. Revision of a tibial baseplate using a customized oxinium component in a case of suspected metal allergy: a case report. *Acta Orthop Belg* 2011;77:691–695.
103. Goto M, Gotoh M, Mitsui Y, et al. Hypersensitivity to suture anchors. *Case Rep Orthop* 2013;2013:932167.
104. Nawaz F, Wall BM. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome: suspected association with titanium bioprosthesis. *Am J Med Sci* 2007;334(3):215–218.
105. Hettige S, Norris JS. Mortality after local allergic response to titanium cranioplasty. *Acta Neurochir* 2012;154:1725–1726.
106. Redline S, Barna B, Tomashefski JF, et al. Granulomatous disease associated with pulmonary deposition of titanium. *Br J Ind Med* 1986; 43:652–656.
107. High WA, Ayers RA, Adams JR, et al. Granulomatous reaction to titanium alloy: an unusual reaction to ear piercing. *J Am Acad Dermatol* 2006; 55(4):716–720.
108. Belohlavek J, Belohlavkova S, Hlubocky J, et al. Severe allergic dermatitis after closure of foramen ovale with Amplatzer occlude. *Ann Thorac Surg* 2013;96:e57-e59.
109. Siddiqi A, Payne AG, DeSilva RK, et al. Titanium allergy: could it affect dental implant integration? *Clin Oral Implants Res* 2011;22(7):673–680.
110. Deas DE, Mikotowicz JJ, Mackey SA, et al. Implant failure with spontaneous rapid exfoliation: case reports. *Implant Dent* 2002;11(3): 235–242.
111. Bilhan H, Bural C, Geckili O. Titanium hypersensitivity: a hidden threat for dental implants? *N Y State Dent J* 2013;79(4):38–43.

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112. Chaturvedi TP. Allergy related to dental implant and its significance. *Clin Cosmet Invest Dent* 2013;5:57–61
113. Keller CA, Frost A, Cagle PT, et al. Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. *Chest* 1995;108(1):277–280.
114. Humble S, Tucker JA, Boudreaux C, et al. Titanium particles identified by energy-dispersive x-ray microanalysis within the lungs of a painter at autopsy. *Ultrastruct Pathol* 2003;27:127–129.
115. Tilsley DA, Rotstein H. Sensitivity caused by internal exposure to nickel, chrome and cobalt. *Contact Dermatitis* 1980;6:175–178.
116. Romaguera C, Grimalt F. Pacemaker dermatitis. *Contact Dermatitis* 1981;7(6):333.
117. Suhonen R, Kanerva L. Allergic contact dermatitis caused by palladium on titanium spectacle frames. *Contact Dermatitis* 2001;44:257.
118. Bircher AJ, Stern WB. Allergic contact dermatitis from "titanium" spectacle frames. *Contact Dermatitis* 2001;45:244–245.
119. Thomas P, Thomas M, Summer B, et al. Impaired wound-healing, local eczema, and chronic inflammation following titanium osteosynthesis in a nickel and cobalt-allergic patient. *J Bone Joint Surg Am* 2011; 93:e61(1–5).
120. Lim H-P, Lee K-M, Koh Y-I, et al. Allergic contact stomatitis caused by a titanium nitride-coated implant abutment: a clinical report. *J Prosthet Dent* 2012;108:209–213.
121. Coulter I, Lee M, Zakaria R, et al. Pin site allergic contact dermatitis: an unusual complication of halo fixation. *Br J Neurosurg* 2012; 26(4):566–567.
122. Oliva X, Oliva J, Oliva JD. Full-mouth oral rehabilitation in a titanium allergy patient using zirconium oxide dental implants and zirconium oxide restorations: a case report from an ongoing clinical study. *Eur J Esthet Dent* 2010;5(2):190–203.
123. Pastides P, Chimutengwende Gordon M, Maffuli N, et al. Stem cell therapy for human cartilage defects: a systematic review. *Osteoarthritis Cartilage* 2013;21:646–654.
124. Peeters CMM, Leijs MJC, Reijman M, et al. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review. *Osteoarthritis Cartilage* 2013;21:1465–1473.
125. www.clinicaltrials.gov [database online]. Bethesda, MD: National Institutes of Health National Library of Medicine; February 29, 2000. Updated daily. Accessed August 10, 2014.
126. Thyssen JP, Jakobsen SS, Engkilde K, et al. The association between metal allergy, total hip arthroplasty, and revision. *Acta Orthop* 2009; 80:646–652.
127. Swiontkowski MF, Agel J, Schwappach J, et al. Cutaneous metal sensitivity in patients with orthopaedic injuries. *J Orthop Trauma* 2001;15:86–89.
128. Crawford GH. The role of patch testing in the evaluation of orthopedic implant-related adverse effects: current evidence does not support broad use. *Dermatitis* 2013;24:99–103.
129. Schalock PC, Thyssen JP. Metal hypersensitivity reactions to implants: opinions and practices of patch testing dermatologists. *Dermatitis* 2013; 24(6):313–320.
130. Thomas P, Schuh A, Ring J, et al. Orthopedic surgical implants and allergies: joint statement by the implant allergy working group (AK 20) of the DGOOC (German Association of Orthopedics and Orthopedic Surgery), DKG (German Contact Dermatitis Research Group) and DGAKI (German Society for Allergology and Clinical Immunology). *Orthopade* 2008;37:75–88.
131. Razak A, Ebinesan AD, Charalambous CP. Metal allergy screening prior to joint arthroplasty and its influence on implant choice: a Delphi consensus study amongst orthopaedic arthroplasty surgeons. *Knee Surg Relat Res* 2013;25(4):186–193.
132. Thyssen JP, Menne T, Schalock PC, et al. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. *Br J Dermatol* 2011; 164:473–478.
133. Schalock PC, Menne T, Johansen JD, et al. Hypersensitivity reactions to metallic implants-diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis* 2011;66:4–19.
134. Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. *Biomaterials* 2005;26:1019–1026.

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