Present Status of the Effectiveness of the Patch Test Reagent for Titanium Hypersensitivity

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Abstract: Titanium and titanium alloys have been used for dental implants, due to their excellent biocompatibility and suitable mechanical properties. The frequency in use of titanium and titanium alloys for dental applications has gradually increased. For example, in 2020, a Japanese insurance approved the use of pure titanium for posterior molars as a metallic cast crown. Titanium alloys have also been used for frameworks of removable partial denture. Allergic reactions to titanium and titanium alloys are rare but do occur. One theory of unexplained implant loss is that the patient is hypersensitive to titanium. The hypersensitivity causes an inflammatory reaction to the implant body and failure to osseointegrate, resulting in implant failure. The patch test for diagnosis of titanium hypersensitivity has been unreliable because the result of the patch test does not match the clinical symptoms. Standard titanium reagents for patch tests are needed for accurate diagnosis of titanium hypersensitivity to prevent the failure of implants.

The objective of this review was to evaluate literature reporting the status of allergic diagnosis for titanium hypersensitivity and analyze the results mentioned. Based on these results, a possible standardization of the titanium reagent for the patch test were discussed. These searched literatures indicated that further national and/or registry based studies will be needed to better inform clinical practice and to identify the scale of metal sensitivity, clear diagnostic criteria, and long-term clinical performance data on hypoallergenic implants.

Keywords: Implant, Metal allergy, Titanium, Patch test reagent, Guideline.

1. INTRODUCTION

Recently, in Japan, patients with allergic disease including atopic dermatitis and allergic rhinitis are increasing [1]. The Japanese Ministry of Health, Labour and Welfare, in 2011 called for"basic guidelines about the promotion of countermeasures for allergic disease estimating that approximately half of the total population in Japan is presenting with some kinds of allergic disease [2].

In the medical and dental fields, devices made of titanium have been used as the biomaterials for the replacement of biomaterials containing nickel and chrome, which have more frequent allergic reactions. This has been attributed to titanium's properties of high corrosion resistance, excellent biocompatibility, mechanical properties, and the development of manufacturing methods [3].

The increase in use of titanium and its alloys for medical, dental and consumer products, for example, pacemaker, orthopedic implants, dental implants and prostheses, cosmetics, personal care, food additives, jewelry, glasses, and golf clubs, is rising. A concern for the increase in exposure to titanium may increase the number of patients with titanium hypersensitivity in the future [4]. In order to become allergenic, metal ions combine with native proteins to form antigenic hapten complexes. These complexes are then processed by antigen-presenting cells and presented to T-cells. Sensitization typically occurs through contact with skin but could also theoretically occur through systemic exposure through ingestion of the food or corrosion of a metal [5].

A hypothesis for unexplained dental implant failure is that the patient may be hypersensitive to titanium. This hypersensitivity causes inflammation and allergic reaction around the dental implant which prevents osseointegration [6]. Therefore, before performing titanium implantation to patients, it would be important to screen for hypersensitivity to the metals to increase the success rate of treatment [7]. Generally, patch testing is the standard procedure to diagnose contact allergy resulting from type IV hypersensitivity [8]. This *in vivo* test aims to reproduce the elicitation phase of

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E-ISSN: 2311-8695/23

the reaction to a contact allergen, that is, allergic contact dermatitis. The patch test is performed by applying allergens under occlusion on the skin under standardized conditions.

There is no standard diagnostic patch test for titanium and therefore a number of different titanium salts are currently used (*e.g*., titanium dioxide, calcium titanate, titanium bis dihydroxide at patch test concentration 10-20%). As titanium has still not yet been confirmed as a sensitizer, it is not possible to distinguish true negative from false negative [9]. At this time, the patch test results for titanium hypersensitivity have not been easy to compare. This is the reason why there remains no reliable patch test for titanium hypersensitivity.

One of studies often cited for titanium allergy in 1500 dental implant patients was reported by Sicilia *et al*. (2008) [10]. They extracted 35 subjects from a 1,500-patient group with titanium allergy and a 800-patient group without titanium allergy were patch tested for titanium allergy. The titanium regents used were TiO_2 petrolatum (pet.) and TiO_2 aqueous (aq.), both 0.1% and 0.5% solutions. Positive reaction to titanium and the other metals were 0.6% in allergy compatible response group and 5.3% in predisposing factor group, respectively. The half of patients who showed the allergic reaction after implant placements, presented positive reaction to titanium reagents before the surgery. It indicated that the patch tests performed before implant treatment might be predictable for allergic reactions to titanium. Especially, so for individuals with a previous history of metal allergy, allergic symptoms after implant surgery including unexplained implant failures, and extensive surgical exposure to titanium.

Several reviews were published indicating results for the titanium patch testing before 2013. After that, few reviews were found regarding the titanium patch test reagents. The purposes of this study was to summarize present status regarding titanium patch testing by performing the literature search using the database with three keywords, titanium, patch test and last 10 years and to propose the baseline for setting the future guideline of the titanium patch test.

2. MATERIALS AND METHODS

This is a non-systematic review. A literature search in the database PubMed, Scopus and Google Scholar up to October 15, 2022, using the following search keywords, titanium, patch test and last 10 years was conducted. Sixty-seven articles were identified. Fifty-five articles could be excluded by reviewing the title and abstract leaving 12 articles to be discussed for this review and to be listed in Table **1**.

3. RESULTS

3.1. Subjects

In these 12 articles, patch tests were used to confirm a suspicion for titanium allergy in approximately more than 100 patients and/or healthy people. Within 12 articles in Table **1**, only 8 articles performed the patch test to both patients that present with and without reported allergy. Therefore, this review was focused on these 8 articles.

3.2. Patch Test Results

From 2013 to 2022, 8 articles were selected and listed below, that included the aim of the developing a rational approach to patients who present with and without titanium allergy. Positive reaction of the patch testing for patients and controls were 0-5.9% and 0-8.5%, respectively. Since, the titanium reagents used were different in each facility, the rates of the hypersensitivity for titanium were also different.

Vermes *et al*. (2013) [11] examined the reactivity of peripheral human leukocytes to various metal ions before hip replacement in order to investigate implant induced metal sensitivity. Three groups, 1) individuals with no implants and no history of metal allergy (7 cases), 2) individuals with no implants and known history of metal allergy (7 cases), and 3) patients undergoing cementless hip replacements (40 cases) were studied using skin patch test. Implants used were Ti-6Al-4V stem, Co-Cr acetabular head and ultrahigh molecular weight poly-ethylene acetabular liner and with Ti-6Al-4V alloy shell. Patients had no other implants. Group three after surgery, all hip implants remained functional and did not need removing. Meanwhile results of patch test with 5.0%, 1.0% and 0.5% (pet.) of $Ti(C_2O_4)_2$ showed no differences among all the groups.

de Graaf *et al*. (2018) [15] evaluated alternatives for titanium dioxide as a patch test preparation, and to profile titanium reactions and manifestations conducted with 458 patients (248 patients suspected titanium allergy, 163 patients suspected metal allergy and 47 controls) who underwent patch testing with at least 1 of 5 different titanium salts [titanium oxalate hydrate (pet.), titanium isopropoxide (pet.), titanium citrate (pet.), titanium lactate (pet.) and titanium dioxide (pet.)].

Table 1: Patch Tests for Titanium Hypersensitivity

Year	Country	Author	Subjects or patients	Subjects or patients No.	Test solution	Conc.	Reading days	Positive No.	Comments	Ref. No
2013	Hungary	Vermes et al. 94	Controls with no implant	7	$Ti(C_2O_4)_2$ pet.	0.50%	2, 3, 4 and 7	0	Patch testing at 3, 6, 12, 24 and 36 months. Various responses have been reported to titanium as well, and cross-reactivity between nickel and cobalt is known. The result of combined leukocyte assays can be a useful tool to test implant materials-related reactivity and may be superior to patch testing. These tests provides the possibility only for secondary or tertiary preventation. a screening process where susceptibility for orthopedic implant-induced metal hypersensitivity can be determined before joint replacement providing possibility for primary prevention.	11
			Patients with no implant and with a history of MHS	7		1.00%				
			Patients with no history of MHS pre-implantation	40						
			Patients with no history of MHS post-implantation of Ti-containing implant	40		5.00%				
2014	Denmark	Gustafson et al. 43	Patients with metal on metal (MOM) total hip arthroplasties	19	titanium dioxide	10.00%	4	2 cases	The results for the patch test showed no significant differences. The longer-term metal exposure should be investigated.	12
			Patients with metal on polyethylene (MOM/COP) total hip arthroplasties	24				0		
2015	China	Zhang et al. 92	patients received alloy restoration in the oral cavity	92	TiC_2O_4 pet.	5.00%	2, 3 and 7	5.0%	Patch test is necessary in diagnosis of contact allergy. Prior to restoration, a patch test for hypersensitive patients is recommended, and the use of different metal alloys in the same patient requires caution.	13
2017	Lithuania	Linauskiene et al. 546	Patients suspected allergic contact dermatitis (ACD)	546	titanium pet.	10.00%	3, 4 and 7	0	No sensitization to titanium was found.	14
					Ti dioxide pet.	10.00%				
					Ti oxalate pet.	5.00%				
					Ti nitride pet.	5.00%				
2018	Netherlands	Graaf et al. 458	Patients suspected titanium allergy	248	Ti(IV) oxalate hydrate pet.	5.00%	2, 3, and 7	8 cases	Ti(IV) oxalate hydrate pet., Ti(IV) isopropoxide pet., Ti citrate pet., Ti lactate pet. and Ti dioxide pet. Were examined.	15
					Ti(IV) isopropoxide pet.	100 ppm		1 case		
						1.00%		4 cases		
						5.00%		1 case		
						10.00%		2 cases		
					Ti citrate pet.	0.16%		1 case		
						0.32%		1 case		
					Ti lactate pet.	0.16%		2 cases		
					Ti dioxide pet.	as is		1 case		
			Patients suspected metal allergy	163	Ti(IV) oxalate hydrate pet.	5.00%		0		
					Ti(IV) isopropoxide pet.			0		
					Ti dioxide pet.	as is		2 cases		
			controls	47	Ti(IV) oxalate hydrate pet.			2 cases		
					Ti(IV) isopropoxide pet.			0		
					Ti citrate pet.			0		
					Ti lactate pet.			0		
					Ti dioxide pet.	as is		0		
2018	Japan	Hosoki et al. 270	patients suspected Dental metal allergy	270	$TiCl_4$ aq.	0.10%	2, 3 and 7	5.9%	An examination of pre-implant patients who have a history of hypersensitivity reaction to metals.	16
						0.05%		1.5%		
					TiO_2 pet.	30.00%		0.4%		
						10.00%		0.0%		

Year	Country	Author	Subjects or patients	Subjects or patients No.	Test solution	Conc.	Reading days	Positive No.	Comments	Ref. No
2018	Switzerland	Furrer et al.	Pre-operative (PO)	73	Titanium Chloride aq.	0.10%	2, 3 and 6	0	Establishment of the relevance of a positive patch test reaction in implant patients is particularly challenging. There is a lack of standardization and validation of patch test preparations with metals such as Ti, V and Nb, which rarely elicit delayed hypersensitivity. This may lead to an overestimation of the irritant potential of metals, and an underestimation when the optimal test conditions are not established. 15.5% of the patients with a Ti-containing implant had a positive patch test reaction to Ni	17
		311			Titanium pet.	10%		0		
					Titanium nitride pet.	5%		0		
					Titanium oxalate decahydrate pet.	1%		0		
			Osteosynthesis (OS)	31	Titanium Chloride aq.	0.10%		0		
					Titanium pet.	10%		0		
					Titanium nitride pet.	5%		0		
					Titanium oxalate decahydrate pet.	1%		0		
			Hip total prosthesis (HTP)	28	Titanium Chloride aq.	0.10%		0		
					Titanium pet.	10%		0		
					Titanium nitride pet.	5%		0		
					Titanium oxalate decahydrate pet.	1%		0		
			Knee total prosthesis (KTP)	175	Titanium Chloride aq.	0.10%		0		
					Titanium pet.	10%		0		
					Titanium nitride pet.	5%		0		
					Titanium oxalate decahydrate pet.	1%		0		
			Shoulder total prosthesis (STP)	4	Titanium Chloride aq.	0.10%		0		
					Titanium pet.	10%		0		
					Titanium nitride pet.	5%		0		
					Titanium oxalate decahydrate pet.	1%		0		
2019	Japan	Kitagawa et al. 1125	patients	925	Ti sulfate pet.	0.10%	2, 3 and 7	5.20%	In patch testing performed before dental implantation, several patients were sensitized to Ti. Therefore, these findings suggested that performing metal allergy testing before dental treatment may decrease the risk for diseases caused by dental implants. The results indicating the existence of Ti-positive patients will be useful for the further progress of dental care.	18
					Ti chloride pet.	0.10%				
					Ti dioxide pet.	0.10%				
			patients before undergoing dental implant	300	Ti sulfate pet.	0.10%		2.70%		
					Ti chloride pet.	0.10%				
					Ti dioxide pet.	0.10%				
2019	USA	Haddad et al. 100	patients with dermatitis	60	Titanium oxide pet.	0.10%	2 and 4	1 (2%)	No significant differences between patients with and without dermatitis. Additional research is also needed to determine why some individuals with documented metal sensitivity appear to suffer more symptomatic complications than others with the same preoperative profile. Further research is needed to better identify and describe the varying manifestations of metal allergies and to help guide postoperative treatment in the setting of likely metal allergic hypersensitivity.	19
			Patients without dermatitis	40		0.10%		0		

Year	Country	Author	Subjects or patients	Subjects or patients No.	Test solution	Conc.	Reading days	Positive No.	Comments	Ref. No
2019	China	Sun et al. 207	Patients planned for titanium alloy cranioplasty	207	Titanium Chloride pet.	2%	2 and 3	0.00%	Patients having multiple metal hypersensitivities in patch tests, particularly for those who had confirmed allergies to 4 or 5 metals, had a statistically significantly higher chance of developing implant failure. Further investigations with larger sample sizes are required. Randomized controlled trials with larger sample sizes have been proposed to better evaluate how patch testing could sensitized individuals to react to a metal implant.	20
2020	Croatia	Zigante et al. 228	subjects no symptoms undergoing orthodontic treatment	228	titanium pet.	10%	2, 4 and 7	9 (4%)	Allergic sensitization to titanium occurs more than expected and therefore should not be overlooked. There are no clear symptoms related to allergic sensitization to titanium and nickel. Titanium allergy needs to be further investigated.	21
					Ti dioxide pet.	10%				
					Ti oxalate pet.	5%				
					Ti nitride pet.	5%				
2021	Turkey	Ozden et al. 110	Patients with recurrent aphthous stomatitis (RAS)	36/63	Ti dioxide pet.	10%	2, 5 and 7	2 (5.6%)	Titanium dioxide in toothpaste is suspected as allergens. However, no significant differences between patients and controls	22
			Healthy controls	47	Ti dioxide pet.	10%		4 (8.5%)		

No titanium-specific risk factors and clinical picture could be identified. Titanium dioxide seemed to be inadequately sensitive for identifying titanium allergy. They suggested that titanium salts seem to be possible superior patch test preparations, but appear to be unsuitable if used singly.

Furrer *et al*. (2018) [17] evaluated sensitization to implant materials in patients with implant-related complications, to identify allergens, and to clarify whether hypersensitivity was a relevant cause. As for the titanium patch test, titanium powder (10% pet.), titanium chloride (0.1% aq.), titanium nitride (5% pet.) and titanium oxalate decahydrate (1% pet.) were used. Even though, a positive patch test reaction to other metal was seen in 64.4% of preoperative patients and in 54.6% of patients with implant-related complications, no positive reaction to titanium was observed for patients and control groups. They concluded that titanium patch test rarely elicits delayed hypersensitivity, therefore, these results might lead to an overestimation and or underestimation when standard optimal patch test conditions for titanium are not established.

Sun *et al*. (2018) [18] prospectively investigated the prevalence of metal hypersensitivity in 207 patients for whom cranioplasty was planned and assessed its relationship with titanium implant failure caused by exposure. Titanium chloride (2% pet.) was used as titanium reagent. No allergy to titanium was detected in this study. The overall incidence of cranioplasty implant failure was 5.31% (11 of 207). Patients showing hypersensitivities to more than 3 kinds of metal had higher risks of titanium plate exposure. Based on their findings, the authors suggest that routine allergy screening be performed before titanium plate cranioplasty. In addition, patients with hypersensitivity to more than 3 metals, alternative materials should be considered for cranioplasty.

Kitagawa *et al*. (2019) [19] analyzed dental metal allergy in 1225 patients, including 300 who were scheduled to undergo dental implant surgery. For diagnosis of metal allergy, patch tests using metal allergens were performed. In this study, 0.1% (pet.) of titanium sulfate, titanium chloride and titanium oxide were prepared for diagnosing the titanium hypersensitivity. The results showed that positive patch test reactions to the titanium were 5.2% in the patient group and 2.7% in undergoing implant group, respectively. This finding suggested that metal allergy tests performed before dental treatment might decrease the risk for developing a symptom caused by metal implants.

Haddad *et al*. (2019) [20] evaluated the prevalence of metal allergies in a subset of the population and reviewed the significance through a survey of the current literature. A hundred patients were referred for metal allergy test, 46 of whom were for reasons related to planned orthopedic surgery. Of those tested, 60 patients had a history of dermatitis and 40 did not. Titanium oxide (0.1% pet.) was used as the titanium

reagent. Only one of the 60 patients showed positive reaction to titanium. Some individuals experience more notable allergic reactions to implanted devices than others. Localized and generalized skin reactions have been reported, along with implant failure and loosening. They concluded that additional research is also needed to determine why some individuals with documented metal sensitivity appear to suffer more symptomatic complications than others with same preoperative profile.

Zigante *et al*. (2020) [21] evaluated how much self-reported symptomatology, age, and sex are predictors of titanium and nickel allergic sensitization in patients in treatment with fixed orthodontic appliances. The study analyzed 228 adolescent subjects. The allergic sensitization testing included epicutaneous patch test to titanium (10% pet.), titanium dioxide (10% pet.), titanium oxalate (5% pet.), titanium nitride (5% pet.), and nickel sulfate (5% pet.). Prevalence of the allergic sensitization to titanium in patients undergoing orthodontic treatment was 4% while to nickel 14%. Hypersensitivity to both metals at the same time was present in 2% of subjects. They concluded that allergic sensitization to titanium and nickel are not very frequent in orthodontic patients, and self-reported symptomatology is a weak predictor of those sensitizations.

Ozden *et al*. (2021) [22] studied whether the skin patch test can be used to determine if toothpaste allergens play a role in the etiology of recurrent aphthous stomatitis (RAS). Sixty-three patients with RAS and 47 healthy volunteers were performed patch tested with sodium lauryl sulfate, propylene glycol, aluminum chloride hexahydrate, menthol, triclosan, and titanium dioxide (10% pet.), which are contained in most of the toothpastes. Sodium lauryl sulfate, titanium dioxide, and menthol showed the most common positive allergens in both groups. The skin patch test was positive in 22% of subjects with RAS and 23.4% of the controls. Differences between groups was not statistically significant. In order to determine a clearer relationship, a study in a larger patient series employing intraoral patch testing with more toothpaste ingredients will be suggested.

In most of the articles studying the titanium patch test, titanium powder in petrolatum , titanium dioxide in petrolatum or aqueous , titanium (IV) oxalate hydrate in petrolatum , titanium (III) nitride in petrolatum have been prepared and applied for the patch test reagents. Also, titanium chloride in petrolatum or aqueous and titanium sulfate have been used. The concentration of the reagents ranged 0.1% to 10%. Along with different concentrations, the pH of reagents ranged pH 4.5-7.5. One of the studies reported that the skin reaction by the different salts of the titanium compound cannot be ignored as the influence of reagent itself on skin [9] . As mentioned, the various types of the reagents have been selected as the reagents, but not standardized. Note that the different groups that performed the patch tests using different titanium reagents, the results were not easily comparable to each other. However, some tendencies were that reaction to 5.0% pet. of titanium (IV) oxalate hydrate and 0.1% in pet. or aq. of titanium chloride became higher in comparison with other reagents.

As for the evaluation, variability in time of reading the patch tests was prevalent. Three and seven days later were common for the evaluation. Some of the studies reviewed, evaluated only at three days later and/or four days. Since the diagnosis for a delayed hypersensitivity allergy may take up to seven days, a question remains whether these delayed hypersensitivity reactions were missed. A recommended standard observation period would be advantageous.

Most of the researchers have been adjusting the type and concentration, by trial and error to establish the guideline for the titanium reagents. At the moment, it is not easy to compare the patch test results due to the different circumstances of each study. In other words, no standard patch test for titanium has been established in the literature and would be helpful. Research has recommended the necessity to better detect, identify and describe the varying manifestations of metal allergies and to help guide postoperative treatment in the setting of likely metal allergic hypersensitivity.

4. DISCUSSION

The incidence of titanium hypersensitivity has been increasing with the increased use of titanium as implant materials. After implant placement, several symptoms including allergic reaction and unexpected implant failures were reported. The cause of these symptoms was thought to be an allergy to titanium. Generally, allergic reactions to metals in implants display distinct characteristics of delayed-type (type IV) hypersensitivity. Patch testing is the most widely used *in vivo* method to diagnosis the type IV sensitivity reactions to potential contact allergens [23, 24]. Unfortunately, despite positive and/or negative patch

test results, sometimes the removal of the implant device and relief of symptoms was the definitive diagnosis for titanium hypersensitivity [25]. Guidelines and development of a standard titanium patch test, that could diagnose Type IV delayed hypersensitivity without the removal of the implant would be a goal.

Almost all the studies in the literature concluded that there is a need for the establishment of a standard patch test for titanium. In addition, further research will be required to better identify and describe the varying manifestations of metal allergies and to help guide postoperative treatment in the setting of likely metal allergic hypersensitivity.

This review tries to propose the main points for establishment of guidelines for a titanium patch test for the diagnosis of hypersensitivity.

4.1. Procedure of the Patch Test

1. Standardized informed consent for patch testing: Patients should be informed about the purpose and benefits of patch testing, how patch testing is undertaken, and symptoms that may occur. Informed consent would also include patch testing materials, techniques, test series, readings, final evaluation, individual factors that may influence the outcome of the tests, and potential side-effects.

2. Administration of questionaries. These are used for self-reporting of symptoms during the patch test.

3. Patch tests are administered under the supervision of a physician. Cleaning the skin by wiping with cotton wool soaked in alcohol in order to degrease it. The allergens are applied on the upper arm skin and the upper back for two days. It is recommended that the patient takes a shower or bath in the morning before testing.

4. Putting an allergen on the patch test unit. Finn Chamber® (Smart Practice, Phoenix, AZ, U.S.A.) and/ or Patch Tester (Torii Pharmaceutical Co. Ltd. Tokyo, Japan) are patch test devices which provide good occlusion because of the chamber design. Table **2** listed the recommendation for the appropriate amount.

5. The skin can be marked *e.g.*, with nontoxic ink or tape. If the patient can come to the clinic for removal of the tests, the physician has the advantage of using the marked tape for locating the test sites, and no marking of the skin is necessary.

6. Applying the allergens on the upper arm skin or back skin and left under occlusion for 2 days (48 hours). Patients will be instructed to postpone the patch testing for severe or generalized active dermatitis. Patient skin is not too wet or had recent ultraviolet (UV) exposure to the area where the patch tests are applied.

7. Evaluations of the skin reactions will be performed three times, on the second, third and seventh day after applying the patches, as suggested by the manufacturer. The tests should be read not less than 20 minutes after removal. Skin reactions are evaluated according to the ICDRG (International Contact Dermatitis Research Group) by a trained person.

4.2. Selection of the Patch Test Reagents

In many cases, addition of the baseline series appropriate for the patients' geographical location, North American (NA) Standard (the 50 allergens of the NA Standard series; Chemotechnique, Sweden) or American Contact Dermatitis Society's Core Panel, European Baseline Series (Trolab®; Almirall Hermal GmbH, Reinbek, Germany or Chemotechnique Diagnostics, Vellinge, Sweden) is appropriate.

Table 2: The Quantity and Positive Reactions of Each Reagent for a Pad

	Finn Chamber® (8 mm in diameter; area 0.5 cm^2)	**Patch Tester Torii (9 mm in diameter; area 0.6 cm^2)**	**Positive Reaction**
Liquid (aq.)	15 mL 30 mL/cm^2	20 mg 40 mg/cm^2	erythema, infiltration, possibly papules
Petrolatum (pet.)	1 drop	5 mm	weak positive reaction

If the patient is to be evaluated, comprehensive testing should be performed. Patch testing with single allergen or a handful of allergens is not recommended. A single allergen or allergen group (*i.e.*, metals) may not be the only cause of dermatitis.

As a base line series in Europe, the patch test reagents for titanium sensitivity are 5.0% pet. of T-039 titanium (III) nitride and 5.0% pet. of T-041 titanium (IV) oxalate hydrate in The Metal Series MET-1000 (https://www.chemotechnique.se/products/series/metal-series/), and T-040 titanium dioxide and T-042 10.0% pet. of titanium in The Metal Series extended METE-1000 (https://www.chemotechnique.se/products/series/metal-series-extended/). Based on previous research, C-049 calcium titanate (10.0% pet.) , T-039 titanium (III) nitride (5.0% pet.) and T-041 Titanium (IV) oxalate hydrate (5.0% pet.) in Implant Series (IMP-1000) (https://www.chemotechnique.se/products/series/implant-series/) are sold by Chemotechnique MB Diagnotics AB in Sweden.

In The North American Contact Dermatitis Group (NACDG) and Japan, titanium patch test reagents were not approved. Therefore, titanium reagents were prepared at each institution.

In the most of the articles regarding the titanium patch testing, titanium powder in petrolatum, or aqueous, titanium (IV) oxalate hydrate in petrolatum, titanium (III) nitride in petrolatum and titanium chloride in petrolatum or aqueous and titanium sulfate have been prepared and applied for the patch test. The concentration of the reagents have ranged 0.1% to 10%. Some of the literatures have indicated that positive patch test results to titanium are uncommon owing to lack of penetration of titanium salts through the epidermis. Due to low prevalence, diagnosing titanium hypersensitivity is further complicated by lack of a widely accepted screening tool [25].

The literatures used in this review study, showed that titanium dioxide in petrolatum, titanium (IV) oxalate hydrate in petrolatum, titanium (III) nitride in petrolatum and titanium chloride in petrolatum or aqueous were often used for the titanium reagents. Note that the different groups that performed the patch tests using different titanium reagents, the results were not easily comparable to each other. However, some tendencies were that reaction to 5.0% pet. of titanium (IV) oxalate hydrate and 0.1% in pet. or aq. of titanium chloride were higher in comparison with other reagents. On the other hand, one of the studies indicated that titanium powder (TiO_2) cannot penetrate into the tissue and act as hapten due to a passivation layer on the surface [26]. Therefore, titanium dioxide powder in petrolatum should be avoided [27].

In an attempt to establish standard patch tests for titanium, research groups recommended $TiSO_4$ and $TiCl_4$, both 0.1% and 0.2% solutions, as useful reagents for titanium skin patch test [28]. Due to the penetration rate of the TiO_2, it is not recommended to use TiO_2 as a patch test reagent [29].

4.3. Anatomical Site of Patch Test Application

The patch test is performed by applying allergens under occlusion on the skin under standardized conditions.

Generally, the upper back is the preferred site for patch testing due to a flat and large surface for good occlusion and no ultraviolet (UV) exposure. The outer surface of the upper arms or thighs can be used if the back is not suitable for patch testing or is fully used already.

Sometimes, a reaction may vary according to the sites of the patch test is observed [9, 30].

4.4. Evaluation of Patch Test Reaction

Evaluations of the skin reactions were performed three times, on second, forth, and seventh days after applying the patches, according to current practice. Skin reactions were evaluated according to ICDRG standards (Table **3**). However, a negative outcome on a titanium patch test does not exclude the possibility of titanium allergy.

Unfortunately, there are some metal implant cases with clinical symptoms that showed a negative reaction by the patch test. The only way to improve patient symptoms was to remove the metal implant. The reasons of these causes were unclear in literature. It is suggested that the relationship between the patch test reaction and the symptoms should be thoroughly considered in each case [5, 31].

Although 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 to not penetrate the epidermis in healthy [32, 33] or even psoriatic skin [34].

Table 3: Reading Criteria of the ICDRG

Symbol	Morphology	Assessment
-	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, possibly vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g., soap effect, bulla, necrosis	Irritant reaction
NT	No tested	-

Ten points were suggested that could strengthen the suspicion of clinically relevant metal allergy to an orthopedic implant [30]:

1. Chronic dermatitis beginning weeks to months after metallic implantation.
2. An eruption overlaying the metal implant.
3. A morphology consistent with dermatitis (erythema, induration, papules, and vesicles).
4. In rare instances, a systemic allergic dermatitis reaction (characterized by universal dermatitis reactions , typically localized in body flexures).
5. Histology consistent with allergic contact dermatitis.
6. A positive patch test reaction to a metal used in the implant (often strong reactions).
7. Serial dilution patch testing giving positive reactions to low concentrations of the metals under suspicion.
8. Positive *in vitro* test results for metals, for example the lymphocyte transformation test.
9. The dermatitis reaction being therapy resistant.
10. Complete recovery following removal of the offending implant.

4.5. Development of the Guideline

It is important that the national and/or registry-based studies are needed to better inform clinical practice and identify the scale of metal sensitivity, clear diagnostic criteria and long-term clinical performance data on hypoallergenic implants, both in the primary and revision setting. The guideline should indicate that the relationship is unclear between the result of the patch test and the allergic reaction onset, cannot be totally matched, therefore long-term follow-up after the implant operation will be needed.

However, it will be very important that increasing the reliability of the titanium patch test results could be reduce the onset and frequency of postoperative allergy symptoms, and lengthen the life of implants in an aging society.

The conclusions of this review are as follows.

1) Since the incidence of titanium hypersensitivity has increased with increasing use of titanium implant materials, guidelines for a titanium patch test are desired.

2) Some reviews, original articles and case reports were found in the PubMed search. Most literature indicated that it might be difficult to prove titanium allergy using the limited evidence. Sometimes, removal of the implant and cessation of patient symptoms was the only conclusive diagnostic test.

3) Further national and/or registry-based studies are needed to better inform clinical practice and identify the scale of metal sensitivity, clear diagnostic criteria, and long-term clinical performance data on hypoallergenic implants, both in primary and revision setting.

4) For the patient who has planned implants made of titanium materials, it might be important to perform a patch test of titanium before a surgical operation, especially if they have a history of allergy to other metals.

5) If clear evidence that sensitization to certain metals used in dentistry, including titanium, can be identified by a patch test prior to the implantation, guidance should be provided to the clinicians in the selection of implant materials to be used.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ACKNOWLEDGEMENTS

This project was partially supported by a grant from Japanese Dental Science Federation (JDSF-DSP1-2022-301-1) and a Grant-in Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (16K11619, 19K10235).

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Received on 05-08-2023 Accepted on 12-09-2023 Published on 21-09-2023

DOI: https://doi.org/10.12974/2311-8695.2023.11.07