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# Is Allergy to Titanium Bone Fixation Plates a Problem?

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**Abstract:** Open reduction and internal fixation (ORIF) with titanium fixation plates is the gold standard for maxillofacial fracture treatment. Titanium is considered a fully compatible material. However, reports of allergic reactions to titanium implants do occur. The aim of this work is to answer the question whether titanium devices used in the treatment of fractures in the craniofacial region can cause allergic reactions. The study comprised 50 subjects treated surgically for maxillofacial injuries with the use of titanium composite devices. Allergic tests were performed by the patch method. The control group consisted of 20 healthy people who did not have any titanium elements. There were no skin changes to titanium and its compounds in both the test and control groups. Only one patient had a positive skin test which showed an allergic reaction to silver nitrate. Titanium fixing elements, as well as titanium dental implants, according to our research, do not show allergic skin reactions.

**Keywords:** allergy; fracture; osteosynthesis; titanium; patch test; ORIF



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## 1. Introduction

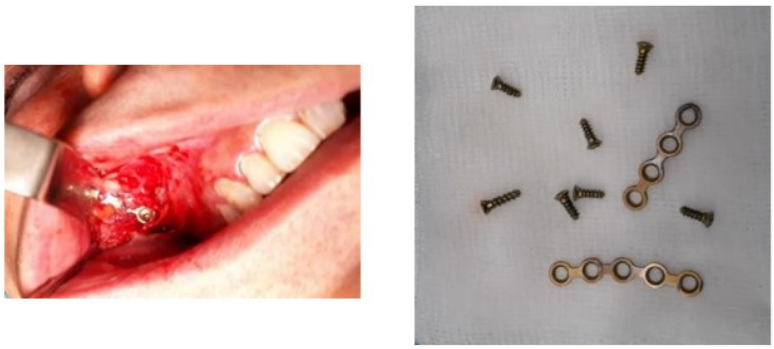
Allergic reaction usually occurs from minutes up to 72 h after repeated contact with an allergen [1–4]. Although allergic contact dermatitis (ACD) rarely constitutes a severe medical condition it may seriously decrease the quality of life [5]. Contact allergy may have a personal and socioeconomic influence on the affected individuals. It is also considered to have an impact on society [5]. Nickel exposure is considered to be the most common cause of contact allergy [6].

Manifestations of ACD include regional skin and mucosal lesions which may be accompanied by asthmatic conditions. Allergic contact stomatitis (ACS) may present as lichenoid lesions or hyperkeratosis, oral erythematous plaques, vesiculation, ulceration, edema, and may also include subjective symptoms of burning sensation, itchiness, or pain [4]. Rarely, lesions extend beyond the oral cavity, involving the facial skin and rest of the body, and resembling those of ACD [7,8]. Many of the materials used in medicine, both metallic and non–metallic, are considered to be associated with elevated risk of allergy [4,9–11]. Chromium, nickel, palladium, copper, and acrylic compounds are known potential allergens [8,10,12,13].

Metals in ionic form can bond with native proteins, forming haptenic antigens, or activating the degranulation of mastocytes and basophiles, leading to type I or type IV hypersensitive reaction development.

Titanium, used widely in dentistry, craniofacial surgery, and orthopedics, was considered fully biocompatible [14–16]. However, the frequency of reported allergic reactions to titanium is increasing [17–20]. Usually in medical applications Grade IV titanium is used, which is composed of titanium, iron, carbon, oxygen, and nitrogen. However, titanium alloys containing vanadium, nickel, aluminum, molybdenum, thallium, and niobium are also used. Titanium use in medicine is increasing; therefore, practitioners of different specialties encounter patients equipped with titanium implants in everyday practice [8,21,22]. Nowadays, open reduction and internal fixation (ORIF), with the aid of titanium hardware

Figure 1a,b, is the gold standard for maxillofacial fracture treatment [23–25]. The influence of titanium allergy on the bone fracture healing process and surgical treatment outcomes remains unclear [26]. In orthopedics postoperative complications associated with titanium allergy are seldom reported [27–29]. Thomas et al. reported fever of unknown origin, impaired wound healing, skin lesions, and fracture treatment failures [27].



(a) (b)

**Figure 1.** Bone plate fixation. (**a**) Hardware placed in oral cavity; (**b**) Hardware after retrieval.

In recent years, fixation with metal hardware has become the most common modality of treatment in post–traumatic bone fractures. The aim of open reduction and internal fixation is to restore the anatomical position of bone fragments and aid in the healing process.

Literature reports type I, III, and IV allergies in the orofacial region, with type IV being the most common in the oral cavity, in which characteristic features of allergy may appear after a few days, or even years, after contact with allergens [30].

The first reports on open reduction internal fixation methods with the use of plates and screws date back to the end of 19th century; however, further advancements in surgical techniques, metallurgy, and hardware design and fabrication were vital for the popularization of this method. It has since become the gold standard for fracture treatment [31,32]. Contemporarily, metallic alloys are widely used in fractures and reconstructive treatment, serving as both temporary and permanent devices.

Metal components used in the facial region may be permanently exposed to the adverse, acidic environment of the oral cavity. This acidity is caused by diet and bacteria, and results in chemical corrosion of metallic components. This results in the release of metal ions, which may circulate in the body or accumulate in local tissue, causing hypersensitivity reactions or tissue damage [10,33]. The hardware used in maxillofacial surgery is primarily composed of stainless steel, nickel–chrome or cobalt–chromium alloys, pure titanium, and titanium alloys [34,35]. The prevalence of contact allergy to metals averages 19.5% in the general population [36].

As a result of advancements in casting and metallurgy, and chemical industry development, titanium is increasingly used in paints, dyes, photocatalysts, and other ordinary items [37]. This, combined with the more frequent use of titanium in medicine, can increase the incidence of titanium allergic reactions [8].

The aim of this study was to determine if there is any relationship between metal hypersensitivity and titanium hardware ORIF surgical treatment outcomes in the maxillofacial region.

## 2. Materials and Methods

The study was carried out among patients admitted to the Medical University of Silesia Cranio–Maxillo–Facial–Surgery Department between 2017 and 2019. The inclusion and exclusion criteria are presented in Table 1.

**Table 1.** Inclusion and exclusion criteria.

| **Inclusion Criteria** | |
|---|---|
| Titanium Hardware Used for Maxillofacial Fracture Fixation<br>Titanium Dental Implants<br>Titanium Patient Specific Implants (PSIs) | |
| **Exclusion Criteria** | |
| **Permanent** | **Temporary** |
| Lack of consent<br>Malignant disease<br>Autoimmune disease<br>Tattoo/skin lesion in interscapular area<br>General disease | Active infectious disease<br>Antiallergic drugs<br>Steroid therapy<br>Extensive sunbathing<br>Cryotherapy<br>Vaccination |

The inclusion criteria were:

- The presence of titanium implants used for maxillofacial fracture fixation; or
- The presence of titanium dental implants; or
- The presence of titanium patient specific implants (PSIs) reconstructing the maxillofacial bone;

and patients signed consent for inclusion in the research.

The exclusion criteria were divided into permanent and temporary. The former consisted of:

- Lack of patient's consent;
- Malignant disease;
- Autoimmune disease;
- Tattoo or skin lesion in interscapular or suprascapular area;
- General disease.

The temporary exclusion criteria included:

- Active infectious disease;
- Antiallergic drugs usage;
- Steroid therapy;
- Extensive sunbathing;
- Cryotherapy;
- Vaccination.

The study enrolled patients with maxillofacial fractures treated in the Craniomaxillofacial Surgery Department with the use of titanium hardware. The study was carried out after completion of fracture treatment, which is 2 to 6 months after surgery. Moreover, the control group was established, and the study was carried out in two groups:

1. Group 1 (research group) (n = 50)—including the patients treated for maxillofacial fractures with the aid of titanium hardware.
2. Group 2 (control group) (n = 20)—comprising healthy subjects with no history of medical titanium usage.

The patients were subjected to:

1. Thorough medical history evaluation regarding prior orthopedic or dental procedures, in which titanium devices were used, and their occupational and environmental exposure to titanium or its compounds;
2. Clinical examination with emphasis on skin and oral mucosa screening for lesions of ACD or ACS type;
3. Skin allergy test with the aid of patch test.

The skin allergy test was performed using the patch method without breaking the continuity of tissues. The patch skin test was manufactured by Chemotechnique Diagnostics

(Vellinge, Switzerland) in the form of patches containing allergens (titanium nitride 5%, titanium oxide 10%, zinc chloride 1%, titanium oxalate 5%, calcium titanate 10%, and titanium 10%) were placed on the back skin by sticking the IQ chamber in the interscapular or suprascapular area for a 48 h period. Results were collected at 2, 4, and 5 days. In doubtful situations, an additional reading was carried out after 7 days. The readings were graded according to the scoring system introduced by the International Contact Dermatitis Research Group (ICDRG) (Table 2) [38,39]. The research was approved by Medical University of Silesia Local Ethics Board (protocol code KNW/0022/KB1/78/17, date of approval 11 July 2017).

**Table 2.** The International Contact Dermatitis Research Group (ICDRG) clinical patch test reactions scoring system.

| Symbol | Relevance | Clinical Appearance |
|---|---|---|
| ?+ | Doubtful reaction | Faint, nonpalpable erythema |
| + | Weak reaction | Erythema, infiltration, possible papules |
| ++ | Strong reaction | Erythema, infiltration, papules, vesicles |
| +++ | Extreme reaction | Erythema, infiltration, coalescing vesicles; bullae or ulceration |
| – | Negative reaction | No changes |
| IR | Irritant reaction | No induration |
| NT | Not tested | |

## 3. Results

The research group consisted of 50 patients, including 38 males and 12 females. The mean age was 31 years old. Timewise, in 2 cases testing was performed less than 6 months after the titanium implant placement; in 32 cases it was performed between 6 and 12 months after titanium implant placement; in 16 cases the test was performed more than 12 months after the titanium implant placement. Regarding the postoperative complications after titanium miniplate internal fixation, the most frequent was the trigeminal nerve paresthesia (23 cases) and edema (19 cases). In four cases wound dehiscence and hardware exposure were noted. The clinical symptoms are presented in Table 3.

**Table 3.** Clinical symptoms.

| Clinical Symptom | Number of Patients | Percentage (%) |
|---|---|---|
| Surgical complications | | |
| Paresthesia | 23 | 46 |
| Wound dehiscence | 4 | 2 |
| Loss of hardware | 0 | 0 |
| Swelling | 19 | 38 |
| Allergic manifestations | | |
| Eczema on skin | 3 | 6 |
| Mucosal lesions | 2 | 2 |

The allergic reaction is triggered when repeated exposure to the allergen happens. The aim of the research team was to establish any previous contact with titanium–containing agents. In eight cases there was evident prior contact with an allergen, but in 42 cases patients could not deny possible former contact. None of the patients were allergic to titanium or its compounds. Only one patient had a positive patch test for silver nitrate, which was a strong (++) reaction (Figure 2).

Due to unequivocal research results, statistical analysis was not carried out.

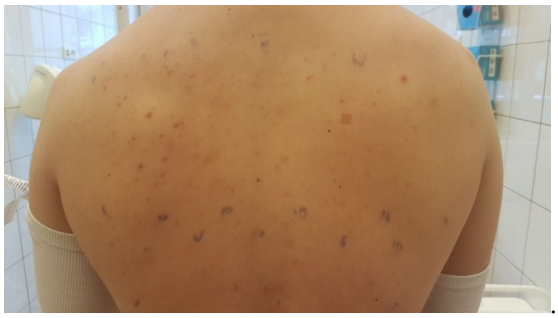


**Figure 2.** Patch test showing positive reaction to silver nitrate.

## 4. Discussion

The literature reports a plethora of clinical manifestations of metal hypersensitivity. Watchmaker and coauthors presented a case report of diffuse, pruritic, pink scaly patches on the trunk and extremities, which developed 3 weeks after placing of a stainless–steel locking fibular plate (DePuy Synthes West Chester, PA, USA) containing 2% manganese used for a lateral malleolus fracture fixation [40].

Allergy due to nickel sensitivity has been repeatedly reported by various authors. Stoddart described a case of anaphylaxis due to a nickel–plated cannula used for transfusion. McKenzie, Aitken, and Ridsdill–Smith reported urticaria related to Vitallium nail insertion and demonstrated that the reaction was caused by nickel, one of the Vitallium alloy components [41–43].

Contact hypersensitivity reactions to stainless steel and cobalt alloys have been described and were associated with chromium, cobalt, nickel, and rarely with molybdenum. On the other hand, titanium is believed not to provoke allergic reactions. Therefore, currently the most used material is titanium and its alloys. Even titanium described as commercially pure titanium supplied for implant manufacturing may be contaminated with nickel during the production process. Schuh et al. inspected the nickel content of commercially available titanium alloys ($TiAl_6Nb_7$, $TiAl_6V_4$) and pure titanium, and reported nickel concentrations of up to 0.034 wt%. Iodide–titanium was reported to have the lowest concentration of nickel (0.002 wt%) [44]. Therefore, corrosion of titanium hardware may release nickel and other trace elements into the tissues.

Although titanium has not been traditionally considered an allergen, cases of allergy to titanium have been reported [45,46]. Investigators of titanium contact allergy found that its incidence rate is about 0.6% [47].

Any occurrence of allergic reaction to biomaterial disqualifies it from clinical use. Although immediate hypersensitivity (Type I) or anaphylactic reactions to biomaterials are extraordinary, chromium and nickel salts–initiated Type I reactions, however these were not directly from implanted biomaterials [48]. The typical presentation of metal allergy in patients after open reduction internal fixation is delayed–type hypersensitivity eczema, which manifests as flare ups at previous patch test sites, exfoliative erythroderma, symmetrical intertriginous and flexural exanthema, and widespread dermatitis [49].

Patients with nickel contact dermatitis were reported to had higher IL–22 blood levels [11].

Patch testing is the preferred diagnostic method for delayed–type hypersensitivity, type IV reactions, and metal hypersensitivity [50,51]. Patient medical history, clinical findings, and the results of patch testing serve typically as diagnostic tools for titanium allergy. However, because of low epidermal penetration, some authors suppose that patch testing is unreliable [52,53]. Therefore, a number of alternative methods for the detection of contact allergy have been proposed—which include lymphocyte stimulation tests. However, there is no agreement on their suitability and reliability, so titanium allergy is diagnosed on the basis of clinical evaluation and patch testing [54]. Reports of delayed–type hypersensitivity date back to 1984 and 1985 when Peters et al. and Verbov, respectively, presented cases of allergic reactions after implantation of a titanium–encased

pacemaker [55,56]. However, the allergology work–ups and patch test preparations are thought to have been insufficient in these studies. Thomas et al. described a case of ORIF treatment with the use of titanium hardware which resulted in impaired fracture healing and localized perioperative eczema. Although no reactions to titanium, nickel, chromium, or cobalt were revealed by patch testing, the lymphocyte transformation test revealed in vitro enhanced proliferation in response to titanium. Moreover, the removal of the titanium hardware resulted in fracture healing and the regression of eczema. Moreover, in vitro hyperreactivity to titanium was no longer observed [27].

In our study, all but one of the patch tests was negative, which may be associated with their low epidermal penetration. On the other hand, the clinical signs of allergy were also infrequent in our patients. This may lead to the hypothesis that observed surgical complications have to be attributed to other, non–allergic, factors. Both the concerns about reliability of the patch tests, and the relatively small sample size, constitute the limitations of this study.

Gingival hyperplasia around dental implants and chronic inflammation in the tissues surrounding titanium hardware were reported by Mitchell, but without proper allergology work up [57,58]. One case of ACD after placement of a dental implant in the maxilla was reported by Pigatto et al. Two cases of ACD after usage of titanium hardware in foot and metacarpal bone fractures were reported by Darlenski et al. [51,59]. Moreover, Oki Suwarsa described the case of systemic erythema with itching 7 days after ORIF treatment of a mandibular fracture with the aid of titanium hardware [60].

Certainly, the association between corrosion of titanium hardware, release of titanium particles, and the failure of implants is present; but the data are scarce, and no definitive statements can be made. The aforementioned reports of contact dermatitis or granulomatous reactions to titanium prove that further research is essential for clinical success.

## 5. Conclusions

According to the findings of our research, the complications of ORIF are unlikely to be associated with titanium allergy.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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