Type IV Titanium Hypersensitivity: Rare, or Rarely Detected?

Hypersenzitivita IV. typu na titan: vzácná nebo jen vzácně rozpoznaná?

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SUMMARY

The presented review aims to summarize the current knowledge of hypersensitivity to titanium – a material widely used *in medical applications* thanks to its exceptional chemical stability, resistance to corrosion, low specific weight and high strength. The hypersensitivity to metals is usually caused by the Type IV immunopathological reaction. Case reports on allergic reactions to titanium are rare but the actual occurrence can be expected to be much higher, especially due to its problematic detection. Although cutaneous patch tests are widely accepted and used for the diagnosis of hypersensitivity of numerous metals (e.g. Ni), it is notoriously unreliable in case of allergies to titanium, which may be associated with the low percutaneous transport of titanium and its salts. The Lymphocyte Transformation Test has superior sensitivity but it remains mostly unknown among clinicians and there are not many laboratories capable of performing it. This review presents numerous case reports indicating, in combination with the above-mentioned facts, that hypersensitivity to titanium should be considered as a possible cause also in non-specific problems associated with titanium implant failure.

Key words: titanium, allergy, patch test, lymphocyte transformation test.

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INTRODUCTION

Titanium is a grey to silvery-white, light and exceptionally durable metal. Although it is the seventh most common metal in the earth's crust, its mining and subsequent production is very expensive.

The main advantages of titanium and its alloys are their low weight, good mechanical properties, resistance to cryogenic temperatures, chemical resistance to electrochemical corrosion, and biocompatibility. For this reason, they are a sought-after material for use in energy industry, transport, water treatment, liquid and gas transport and medicine (Fig. 1)

As far as commercial utilization is concerned, the most widely used form is not the metal itself but titanium oxide (TiO_2) powder, used as a whitening agent (known as E171). Hence, titanium can be found, among other things, also in food (sweets, especially icing, milk products, etc.), cosmetics (creams, toothpaste), pharmaceuticals, etc., mostly in the form of colloidal anatase and rutile in paints, paper, and plastics (8).

In medicine, titanium is often used in the form of alloys with other metals improving the properties. These can be divided into two categories – alpha stabilizers improving its weldability and temperature stability (aluminium) and beta-stabilizers improving the strength and durability of the implants (vanadium). Titanium and its alloys are subject to rapid surface oxidation leading to the formation of approx. 0.1–1 μm strong passivation layer that prevents deep oxidation. Hence, titanium is highly chemically stable and corrosion resistant even in salt-containing solutions.

Titanium particles can be released from the implant, especially if increased mechanical stress and/or chronic inflammation are present, both of which lead to increased material corrosion. Degradation products arising during corrosion can include besides micro- and nanoparticles also ions and organometallic compounds (6).

Another often mentioned major benefit of the use of titanium in medical applications (most commonly in dentistry, traumatology, orthopaedics, or cardiology) is the extremely rare occurrence of titanium hypersensitivity. It is necessary to mention that all titanium alloys, as well as "pure" titanium, contain a small percentage of other metals, such as aluminium, beryllium, cadmium, cobalt, chromium, copper, nickel, palladium and vanadium. From the metallurgical perspective, these metals constitute just about 1% of the "pure titanium" implants; from the biological perspective, however, even such a small amount can play an important role (16). Nanostructured materials based on titanium dioxide (TiO_2)

have shown great potential for their use in implants, mainly due to their excellent physicochemical properties (such as high specific surface area, ability to elicit a positive cellular response and stability in body fluids). A thin layer of such surface treatment could help reduce undesirable side effects of titanium/titanium alloys implants by preventing or reducing the release of any of the metals present in the implant into organism (21)

The normal titanium serum level is 0.06 μg/L. Several studies reported elevated titanium levels in patients after hip replacement and many times increased levels in case of implant failure. A correlation was also found between the serum concentration of titanium ions and lymphocyte reactivity, which hints at a possible relationship between the ion release and implant failure (27). Other studies focusing on titanium levels in patients with titanium endoprostheses also reported 2x – 98x higher levels of titanium compared to control groups (18).

Hypersensitivity to metals is usually caused by the delayed-type immunopathological reaction (Type IV reaction). The organism is sensitised during the first exposure and a subsequent exposure elicits the response. For the metallic ions to become the allergenic agent, they must bind to a protein, thus forming a hapten complex. Such complex is subsequently captured and presented by antigen-presenting cells (APCs) to T-lymphocytes, typically leading to allergic dermatitis with itching, oedema, erythema, vesicles and, in serious cases, bullae. The incidence of the allergy to metal is 15.5% in the USA; in Europe, it is reported to be even higher, approx. 20%. Nickel is the most common allergen, followed by cobalt and chromium. The occurrence of allergy to metals is higher in women. Systemic contact dermatitis is the most common manifestation of allergy to metals. The original sensitisation is through the skin and if systemic exposure to the allergen subsequently occurs, an eruption appears most commonly at the place of the original contact; however, generalized eczema, dermatitis of the hands, erythroderma, vasculitis-like lesions or intertriginous or flexural exanthema can also develop (2). As already mentioned, hypersensitivity to titanium occurs rarely. It is also necessary to consider the fact that titanium is in applications leading to human exposure almost always accompanied by other metals and a possible reaction to such accompanying metals, which are usually much more common allergens, also needs to be considered.

The presented review aims to summarize the current knowledge of hypersensitivity to titanium – a material widely used due to its exceptional chemical stability, resistance to corrosion, low specific weight and high strength in medical applications.

METHODS

Literature for this narrative review was searched in PubMed using search terms “titanium hypersensitivity” (329 hits) and “titanium allergy” (456 hits). After removing duplicates, abstracts were scanned and 65 papers were identified for a full reading. References in these papers were also scanned and cross-referenced, yielding a total of 35 papers used in this review.

Test for assessment of the hypersensitivity to titanium

Diagnosis of titanium hypersensitivity is, as mentioned above, complicated by several factors: (i) the allergy is extremely rare and (ii) there is no reliable standard method for its detection. At present, there are two types of tests for titanium hypersensitivity detection, namely patch tests and lymphocyte transformation tests.

Patch tests (epicutaneous tests) are widely accepted tools for diagnosing the sensitivity to many metals (e.g. nickel). It is in general the most widely used method of testing for Type IV hypersensitivity and this principle is used for more than 500 allergens. However, titanium test is not in the standard testing panel in Europe and, more importantly, the test is not considered reliable.

The principal problem of this testing method for evaluation of titanium hypersensitivity is represented by the fact that titanium and titanium dioxide do not penetrate the skin barrier, not even in psoriasis. From this perspective, titanium salts, namely TiSO4 and TiCl4, may appear promising.

Metal alloy disk patch testing is another variant of patch tests. Still, it retains the problems with titanium transport through the *stratum corneum* from classical patch tests; moreover, some authors report its sensitivity to be lower than that of standard patch tests. Generally, however, it can be said that at present, there is no valid patch test for the evaluation of titanium hypersensitivity (4).

Lymphocyte transformation test

Lymphocyte transformation test (LTT) is a test potentially capable of changing the situation in testing titanium hypersensitivity. It is based on the in vitro measurement of the proliferative reaction of lymphocytes after exposure to an allergen. Lymphocytes are separated from a blood sample and subsequently cultivated in the presence and absence of the suspected allergen. Radioactive marking is used for the quantification of proliferation. The ratio of the radioactivity in the exposed sample and control, i.e., the so-called stimulation index (SI), is then used for diagnosis. Values below 2 are considered normal, 2 to 3 as possible sensitisation and values over 3 are considered proof of hypersensitivity (4). For verification, morphological analysis of lymphoblast presence is performed.

A modification of LTT called MELISA® (Memory Lymphocyte Immunostimulation Assay) has been patented. The probably most significant modification of this assay compared to the standard LTT was the removal of the monocyte fraction.

LTT testing, however, also comes with disadvantages; these include, in particular, the higher price, limited number of antigens that can be tested and, in particular, limited availability of laboratories capable of performing this test (which is also associated with limited awareness of this method among medical person-

nel). Moreover, it seems that LTT is more appropriate for people who are sensitized and currently exposed to allergens and seems less appropriate for people who are sensitized but not currently exposed to allergens.

On the other hand, unlike the patch test, LTT does not lead to sensitisation of the patient's organism and detects cells of the immune system (i.e., provides a systemic response, not only a local reaction). Most importantly, LTT is considered, in particular where titanium hypersensitivity is concerned, a much more reliable test than patch tests (5).

Other testing options

Other available in vitro tests include leukocyte migration inhibitory factor (LIF), measurement of cytokine release, HLA-DR (Human Leukocyte Antigen – DR isotype) or CD69 (human trnamembrane protein Cluster of Differentiation 69) expression.

LIF measures the migration activity of mixed white blood cells based on the fact that leukocytes migration is slower if they are confronted with allergens. The sensitivity of this test is, however, relatively low.

Vermes et al. investigated leukocyte reactivity to Ti (in addition, reactivity to Ni, Co, and Cr were also tested) before and after the implantation of hip replacement using the leukocyte triple assay approach combining LTT, cytokine(IFN-γ and TNF-α) release and LIF testing (34). 6 months after implantation, 12% of patients showed increased reactivity to titanium; after 36 months, this number increased to as many as 18% of patients.

Høl et al. tested the hypersensitivity to t*i*tanium ions and nanoparticles by measuring expression of cell surface receptors CD69 and HLA-DR, which was supplemented with cytokine profiling (IL-1 β, IL-10, INF-α, IL-6, IL-12, Eotaxin, IL-13, IL-15, IL-17, MIP-1α, GM-CSF, MIP-1p, MCP-1, IL-5, INF-γ, TNF-α, IL-1RA, IL-2, IL-7, IP-10, IL-2R, MIG, IL4 a IL-8) (11). The titanium ions elicited higher reaction than nanoparticles; nevertheless, the reactivity was dose-dependent for both forms. The authors also suggested that the immune reaction was mediated by the monocyte-macrophage system.

Of course, the histological examination of the peri-implant tissue is the last resort for diagnosis. This approach is, however, invasive and associated also with problems such as high time demands and subjective reading.

REPORTED ADVERSE REACTIONS TO TITANIUM

First reports about hypersensitivity to titanium appeared in the 1980s. They were mostly associated with pacemakers, later also with dental implants, osteosynthetic implants, joint replacements, surgical clips, etc. However, only a few larger studies can be found, literature is mostly limited to case reports only.

Probably the most significant and complex study on titanium hypersensitivity is a study by Müller et al. who studied 56 patients with clinical signs of allergic reaction following osteosynthesis with titanium implants (19). Using MELISA, hypersensitivity to 10 metals including titanium was tested in these patients. 21 patients had a positive reaction to titanium only, 16 to titanium and another metal and only 19 patients out of this cohort were without titanium hypersensitivity (in 10 out of these, hypersensitivity to another metal was detected). Patch tests were also performed in all these patients; however, all of these returned negative results. In all patients, the clinical symptoms receded after implant removal. 15 patients were retested after the implant removal and regression of the symptoms and in all of them, LTT test results normalized.

The low sensitivity of patch tests demonstrated in that study was also confirmed by another study with more than 1,000 patients with symptomatic reaction to metals, which was performed at the Mayo Clinic (4). This long-term study (10 years) did not reveal a single patient with titanium allergy using patch tests but, at the same time, no allergen was found in 43% of such symptomatic patients. It is, therefore, possible, that a part of these patients were hypersensitive to titanium but the patch test failed to detect it.

The results described above, therefore, lead us to several conclusions: (a) that there is a large group of patients with symptoms of hypersensitivity to metals in whom we are unable to detect the antigen and (b) that the routinely used patch tests are unsuitable for detecting titanium hypersensitivity. Both these conclusions, together with the generally accepted premise that titanium hypersensitivity is extremely rare, lead us to a crucial question: Is this indeed an extremely rare problem, or is the titanium hypersensitivity much more common and we are just unable to detect it?

Titanium hypersensitivity in various fields of medicine

As mentioned above, the literature on titanium hypersensitivity is mostly limited to case reports. For this reason, this part brings an overview of the cases where titanium hypersensitivity was recognised as a cause of the problems.

Traumatological and orthopedical implants

The published case reports mostly describe cutaneous reactions following the application of titanium materials. The first to mention is a case of a 35-year-old patient in whom a titanium plate was used for osteosynthesis of metacarpal fracture. Following the surgery, exanthema developed on the palms – at first, it appeared on the operated hand, later symmetrically on both hands. The patch test was negative but LTT revealed hypersensitivity to titanium. After the plate extraction (and conversion to external fixation), the exanthema regressed and LTT results returned to normal (31). A similar case was reported of a 69-year-old patient who developed exanthema 6 months after osteosynthesis. Allergy screening using a TiO_2 patch test was negative but a subsequent custom-made test with TiCl4 was positive and following the extraction of the osteosynthetic material as well as titanium dental implants, the eczema disappeared (12, 27). Postoperative development of itching exanthema

(together with fever) was also described in an 18-year-old patient after a hallux valgus surgery in which titanium screws were used. Allergy testing using a custom-made patch test with a thin titanium plate was positive and the symptoms fully regressed after extraction of the osteosynthetic material (35). Another case of exanthema was a 42-year-old female after supraspinatus muscle tendon refixation using a single suture anchor (Ti6Al4V), urticaria spread over both upper and lower extremities and face 2 weeks after surgery. Generalized urticaria and angioedema followed and lasted for 4 months. Multiple diagnostic tests were performed, including respiratory and food allergen panel with negative results, which led to a suspicion of allergy to metals. Elevated concentration of free titanium in serum was detected and following the arthroscopic extraction of the suture anchor, both urticaria and oedema gradually fully regressed (22).

Titanium hypersensitivity can, however, have even much more serious implications as demonstrated in a case of a 25-year-old woman referred for surgical resolution of symptomatic pes planovalgus. Medial calcaneal osteotomy and arthrodesis of the tarsometatarsal joint were performed using two compression headless screws and an LCP plate made of Ti6Al4V alloy. Since the first dressing change, erythema was observed, which gradually progressed into painful oedema and in the fourth week after the surgery, wound dehiscence up to the LCP plate was observed. Subsequently, erythematous reaction was observed on the site of the second wound as well. Standard patch tests detected hypersensitivity to titanium and vanadium. The material was extracted and converted to external fixation; during this second surgery, samples for histological examination ware taken, which revealed obvious marks of acute skin and dermis inflammation without any signs of osteomyelitis. After the conversion, the problems regressed (25). The positivity of the patch test should be pointed out – in such an extreme case, even the patch test proved the reaction.

Lalor et al. reported five cases of patients with hip replacement failure; tissues from the vicinity of the implants were subjected to material analysis. The tissues were shown to contain significant amounts of titanium (only negligible amounts of other metals), the source of which were Ti6Al4V screws used for fixation of the acetabular component and the head of the femoral component. The analysis using labelled monoclonal antigens suggested titanium sensitisation. Standard patch tests for titanium and its salts did not reveal any hypersensitivity in any of the patients; in two patients, however, a cutaneous reaction to a titanium-containing ointment (metanium ointment) was observed (17).

The last case is that of a 46-year-old woman after a total hip replacement using a Ti6Al4V component. She developed persistent dermatitis and X-ray revealed signs of the titanium component release. Patch tests for Ti, Cr, Ni and Co were negative. During revision, the titanium component was re-cemented but after several days, it failed again. After a second revision with the replacement of the titanium component for one made of oxinium, no further problems occurred and dermatitis regressed as well (33).

Pacemakers and other cardiological implants

Several cases of pacemaker intolerance due to a titanium component were reported in the literature. The causal therapy lies in the exchange of the pacemaker or, alternatively, its coating using gold, silicone, parylene or polytetrafluoroethylene (PTFE) (15, 30). Although the manifestations may be only local, the problem is systemic and just a simple change of location of the pacemaker, therefore, does not lead to any improvement of the condition. Similar to the case of osteosynthetic implants, skin manifestations are the most common.

Exanthema developed in a 52-year-old patient with Down syndrome a year after the implantation of a pacemaker, which gradually led to the wound dehiscence up to the pacemaker itself. Lab tests revealed no significant elevation of inflammatory markers; however, a patch test using a titanium plate was positive. After the substitution of the pacemaker with one coated by PTFE, the dermatitis regressed (15). An even more serious condition was described in a patient with recurrent sterile necrosis of soft tissues at the location of the pacemaker generator. After implantation of a generator with gold-plated generator surface, the symptoms regressed (30).

Titanium can be used also in occluders. Belohlavek et al. reported a case of a 40-year-old patient referred for patent foramen ovale (PFO) closure using the nitinol Amplatz occluder. Following implantation, she developed a generalized exanthema resistant to antihistamines. MELISA test was strongly positive to titanium oxide and chloride and weakly positive to nickel. Due to the serious character of the clinical signs, the occluder was surgically removed; the clinical symptoms disappeared within three days of extraction (3).

Dental implants

Several cases of reaction to titanium-containing dental implants have been reported, including facial exanthema, gingival hyperplasia or pain, swelling and erythema surrounding the implants (7, 24).

Some dentists suggest that the occurrence of titanium hypersensitivity in oral implants is underestimated and that it should be considered as a possible cause in cases of rapid exfoliation of Ti implants or implant failure.

Sicilia et al. tested 35 patients with allergic manifestations following implantation of a titanium component or with a personal history of severe allergies. Patch tests for sensitivity to titanium and titanium oxide revealed hypersensitivity to titanium in 9 patients. Of those, four had symptoms typical of allergy (itching, oedema and/or eruptions in the mouth, on the face, chest and/or limbs, oedema of the vocal cords in one case), a spontaneous rapid implant exfoliation was observed in two patients. Two more patients had a history of multiple re-implantations with spontaneous implant failures and the last patient had no allergic manifestation following implantation but had a personal history of a severe allergic reaction (28).

Hosoki et al. investigated a group of 270 patients with manifestations of hypersensitivity to dental metals. Patch tests with 28 possible allergenic metals were performed, including TiO_2 (30%, 10%) and TiCl4 (0.1%, 0.05%). 17 patients (i.e., 6.3%) showed hypersensitivity to titanium or its salts. The prevalence of allergic positive reaction to titanium allergens was lower than to other metals but it was definitely not negligible. No patient showed a positive reaction to titanium only, it was always in combination with another metal; hence, the authors proposed to perform a screening test for titanium hypersensitivity in all patients with a known hypersensitivity to another metal (13).

However, considering the already discussed low sensitivity of patch tests, we suggest to interpret the results more carefully, i.e., that in patients with known hypersensitivity to other metals, care should be taken when deciding about implant material and if any problems arise following the use of any titanium (alloy) implant, the possibility of hypersensitivity to titanium should be considered.

Neurosurgical implants

In neurosurgery, titanium is used in spine stabilization surgery as well as in cranioplasty because of its high strength, low density (and, therefore, low implant weight) and malleability. Moreover, unlike ceramic materials, it does not interfere with imaging method. So far, two serious reactions caused by hypersensitivity to titanium in neuro/spondylosurgery were reported.

The first one was a 19-year-old patient who developed DRESS (**D**rug **R**ash with **E**osinophilia and **S**ystemic **S**ymptoms) with interstitial nephritis after a posterior lumbar fusion using Ti6Al4V. A standard epicutaneous test revealed hypersensitivity to titanium and nickel. Extraction of the material was considered; however, due to the extensive adhesions, the material was not extracted and the problem was resolved by a 6 months long application of corticosteroids (20).

The other case was a 64-year-old patient after cranioplasty who died of diffuse cerebral oedema. The postmortem revealed an increased level of mast cell tryptase and identified a massive allergic reaction without identification of another possible source (10).

Other specialties

A case of two brothers undergoing thoracic surgery (Nuss procedure to correct pectus excavatum) was reported by Sakamoto (26). In the surgery of the first brother, a 23-year-old, the surgery was performed using two titanium bars. Postoperatively, the patient developed fevers, chest pain and pleural exudate (microbiologically negative). No test for titanium hypersensitivity was performed and the obvious allergic reaction was resolved by a long-term corticosteroid treatment that lasted until the extraction of the bars (2 years). The same problems occurred also after the surgery of the other brother and were immediately treated by corticosteroids.

In a 64-year-old man, painful erythematous plaque developed in the retroauricular area following the implantation of a titanium hearing aid implant partly covered with silicone within one week after the surgery. Within a month, the area became necrotic with ulceration and the device was spontaneously extruded, after which the defect resolved spontaneously. The patient had no fever and local bacterial swabs were negative. Patch test revealed reaction to titanium(III) oxalate, with no reactions to other titanium compounds (titanium(III) nitride, titanium dioxide, oxide) (1).

Several cases of pulmonary alveolar proteinosis were reported in patients chronically exposed to titanium particles from titanium-containing fumes. The development of the disease was attributed to those titanium particles; however, the hypothesis was not further investigated and verified (14).

Differential diagnosis

The greatest problem posed by titanium hypersensitivity is, as mentioned above, its difficult detection and differential diagnosis as hypersensitivity to other metals is more common than to titanium. Case of bad wound healing after osteosynthesis using titanium implant was described; however, the titanium hypersensitivity was, in the end, not at fault as the problem was caused by an impurity in the implant (nickel in this case) (32).

A similar problem was described in a 68-year-old woman who developed itching erythema in the region of the scar and subsequently on the body and eyelids following a total knee replacement with a Ti6Al4V component. The allergy, however, was to vanadium, not to titanium and was treated by immunosuppressants. Nevertheless, only patch tests were performed so possible titanium allergy cannot be reliably excluded (23).

An interesting case of a 62-year-old woman was described by Engelhart and Segal who reported a case of a 62-year-old woman who developed allergic exanthema on her limbs, nates and back within 6 weeks following implantation of a titanium alloy plate (Ti6Al4V) due to osteoarthritis of the left metatarsophalangeal joint (9). Biopsy revealed the histopathological picture of Type IV allergic reaction with numerous lymphocytes and eosinophils, which was treated by systemic corticoid administration. After 6 months, the material was extracted ad the exanthema regressed within 3 weeks after that. The epicutaneous test for vanadium was negative, which led to a suspicion of titanium hypersensitivity. Eventually, however, an epicutaneous test for VCl3 was performed and found positive.

Treatment

The clinical picture, risk posed by the allergy and the stadium of wound healing are all important factors for decision about treatment. Conservative treatment consisted typically of corticosteroid or immunosuppressant therapy and local treatment. Material extraction with or without substitution for another material, such as zirconium, gold or oxinium represents the causal surgical approach (33).

Another possibility is to substitute the implant for a coated/plated one, which is mostly used in pacemakers

(24). In traumatology, the extraction of the osteosynthetic material combined with meticulous debridement and conversion to external fixation followed by secondary suture or graft appear to be the best solution.

DISCUSSION

There are not many confirmed cases of titanium allergy. The question remains, whether the reality is indeed as good as we believe it to be. Titanium hypersensitivity is likely to be rare, but it is even more likely it remains largely underdiagnosed. Probably the best argument for the latter is the study by Müller and Valentine-Thon, who confirmed the hypersensitive reaction to titanium in 66% (37 out of 56) of patients with a titanium implant and problems developing after the implantation; however, using patch tests, the hypersensitivity was not detected in any of these patients (19). Although the hypersensitivity was often not associated with symptoms typically associated with allergy to metals, this finding itself indicates that titanium hypersensitivity might indeed be much more common than we believe.

Titanium hypersensitivity usually manifests with some delay after the implantation. So, when a patient presents with idiopathic exanthema, microbial or atopic aetiology will be considered first, followed by a drug reaction. In the next stage, it is likely that patch testing will be performed but the crucial question is how many of such patients are likely to be tested for titanium allergy in everyday practice and even if they were, the result is likely to be negative as there is no reliable patch test for titanium hypersensitivity. Patients with titanium hypersensitivity can present, besides exanthema, also with pain, joint effusion, delayed wound/bone healing, persistent secretion, instability, implant failure, or a chronic defect over the osteosynthetic material. Such symptoms will then likely be believed to result from infection or a technical mistake.

Preimplantation testing is another important topic for discussion. With the gradually increasing number of applications for titanium implants and with population ageing, the number of titanium implants in polymorbid patients keeps increasing. For example, the number of primary total hip arthroplasties in USA is expected to grow by 284% and total knee arthroplasties by 401% in 2040 compared to 2015 (29).

In these patients, the risks associated with re-operation (e.g. replacement of total hip endoprosthesis for one made of a different material) are, of course, significantly higher than in relatively young and healthy individuals. So far, we can only rely on the history of allergy to metals but we are only rarely able to find what metals the patient is allergic to. LTT testing, even though it appears to be the method of choice when diagnosing titanium hypersensitivity after a surgery, cannot be used as a preoperative screening tool as lymphocyte proliferation only occurs when the metal is already present in the patient's body, thus sensitising it.

Coating the implant with a thin protective layer could be a possible solution; however, experience with silicon or parylene is not only positive and this field needs to be the subject of further research before implementation into everyday practice (44).

CONCLUSIONS

This paper aimed to summarize the current knowledge of titanium hypersensitivity. Although it is doubtless that titanium hypersensitivity is diagnosed extremely rarely, the presented evidence indicates that this might be rather a problem of underdiagnosis associated with the unreliability of titanium patch test. The fact that titanium is generally considered to be extremely hypoallergenic and is thus usually not even considered as a possible cause of problems developing after implantation of titanium components. MELISA and lymphocyte transformation tests appear to be highly suitable methods for diagnosing this condition; it is, however, not suitable as a method for preoperative screening.

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