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Review article

IMMUNOTOXICOLOGICAL ASPECTS OF BIOCOMPATIBILITY OF TITANIUM

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ABSTRACT

Titanium (Ti) is a non-essential metal element. TiO_2 is used predominantly in the form of micro and nanoparticles in consumer products, including cosmetics and food. Because of its excellent biocompatibility, the trade-pure titan and its alloys are widely used as an alternative of certain metals in invasive medicine, surgery, dental medicine. Contemporary data concerning the sources of exposure to titanium, immune reactions to Ti alloys, current knowledge and perspectives of diagnosis of sensitization or allergic reactions to titanium are discussed.

Conclusion: TiO_2 is much more stable than pure Ti and alloys used in the implants, that should be taken into account when conducting research and analyzing the results. The evidences of possible toxic effects are insufficient. It is difficult to assess the frequency of Ti allergy due to the uncertainty of diagnostic methods, but it is believed that it is very low. This is supported by the evidence that Ti and TiO_2 (often as NP) doesn't penetrate through healthy skin. Skin patch testing with currently available formulations of Ti and TiO_2 has no significant value in clinical practice, and currently it is assumed that there is no reliable method for diagnosis Ti allergy. The functional analysis of cytokine release and investigation of genetic characteristics could be useful for individual risk assessment in dental implantology. Such studies may also help to investigate separately early and late implant loss, as well as to develop new diagnostic tools.

Key words: titanium, dental implants, biocompatibility, allergic response, cytokines

INTRODUCTION

Titanium (Ti) is a non-essential metal element with atom number 22, silver in color. Found in 1790 in England by William Justin Gregor. Later it was isolated by the German chemist Heinrich Klaproth in the mineral rutil (TiO_2). In 1975 he called the mineral Titanium, in honor of the titans, sons of Uranus and Gaia from the Greek mythology. In 1887 non-pure metallic titanium was manufactured, and in 1938 was developed a method for manufacturing of trade quantities of titan [1].

Despite the fact that titanium cannot be found freely in the nature, it is the ninth most widespread element in the earth crust, and the seventh metal as a whole [2]. Can be found predominantly in the minerals ilmenite, rutile, leukoxen.

TiO_2 is used predominantly in the form of micro and nanoparticles (NP) in consumer products, including cosmetics and food, for obtaining white color and UV protection [3]. Furthermore Ti can be combined with other elements for manufacturing light and sturdy alloys, resistant to corrosion and with very high correlation hardiness/density [4]. Because of the latter and because of its excellent biocompatibility, the trade-pure titan and its alloys are widely used as an alternative of certain metals in invasive medicine, surgery, dental medicine throughout the last three decades [5].

Sources of Ti exposure

Around 95% of the worldwide used Ti is not in his metallic form, but asTiO_2 [6] - pigment, highly valued for his chemical stability, brightness, resistance to UV light and supposed low-toxicity [3, 4, 7]. The physical properties of titanium also made him key material for the development of airplane constructions, jet engines, space ships, rockets, sport devices, and medical implants [8].

Titanium is also widely used in the field of medicine, and dental medicine, with huge percent of success, mainly because of its features- high resistance to corrosion, low toxicity, very low allergic potential, and favorable biological response in contact with human tissue [5, 6, 9]. It is believed that the favorable bio-response is due to the restricted ion liberation, stability of the formed alloys and restricted bio effects of the ions. In contact of the titanium with air oxygen, immediately a layer of titanium dioxide is formed with 4 mm thickness, which is powerful barrier against the metal decay. Therefore, according to some authors, this chemical inert layer of titanium dioxide is responsible for the bio-features of the titan in the human body [6, 10, 11]. Strietzel et al inform about release of titanium ions in the presence of fluoride and recommend avoiding the use of fluorides in presence of titanium implants in the oral cavity [12].

Implantology

Titanium is the material of choice in reconstructive (plates, screws) and cardiovascular surgery (pacemakers, stents). Ti and his alloys are widely used for manufacturing of orthopedic implants (artificial joints) [5], due to its great biocompatibility and relation hardiness/density.

Titanium and its alloys are successfully used and are standard materials development dental implants, made of trade titanium or titanium alloys. The layer of titanium oxide allows apposition of physiological liquids, proteins, hard and soft tissues to the metal surface [13].

For orthodontic devices, fixed to teeth which are not in contact with blood or bone, iron and nickel-Ti are used. For fixed to teeth crowns and bridges a lot of alloys, including Ti ones are used. The alloy Ti-6A1-4V was initially used in space industry, and now together with the commercially pure titanium (CpTi) are the most used materials for medical and dental implants. In joint prosthetics, the switch to non-cemented implants changed the exposure to stainless steel and Co-Cr-Mo implants [Fe^{3+}, Ñi^{2+}, Cr^{3+}, Ni $^{2+}$, Cr^2O^3, ÑiÎ, Cr (ÎÍ) 3, Co (OH) 2] towards Ti oxide alloys (Ti $^{5+}$, Al $^{3+}$, TiO_2, Al_2O_3) [14].

Commercially pure titanium is used mainly for dental implants. Pure titanium consists of 99,5% titanium, 0,5% intermediate elements (carbon, oxygen, nitrogen, hydrogen, iron) and the ratio between these elements directly corresponds to the quality of the metal. According to the American Society of Testing and Materials (ASTM) the standard F1295 puts titanium into different classes according to its purity, evaluated according to the amount of oxygen presenting. Currently there are 4 classes CpTi and one titanium alloy, specially developed for dental implants. According to ASTM classes from 1 to 5 are defined. Classes 1 to 4 are unalloyed and are defined as pure titanium; class 5, alloyed with 6% aluminum and 4% vanadium (Ti6A14V) is the strongest one [15]. It is important to note that the so-called CpTi contains impurities of other metals, for example nickel, which could be of clinical importance [16].

Jewelry

Titanium was used in jewelry, especially for production of earrings, piercing etc. since decades [17, 18]. Most often used alloy is Ti-Al-V, as well as CpTi. Ti could be alloyed with gold for obtaining high-carat gold. Hamann et al. [17] examined 956 components of metal jewels in Europe, USA, Japan by X-ray fluorescence spectroscopy. Approximately 4% of them contain Ti, with average concentration 23%.

Cosmetics and personal hygiene products

In the form of dust, titanium is one of the whitest substances, which makes it important component of wide array industrial and consumer products, including cosmetics and sunscreens. The usage of nanosized TiO_2 is expected to grow exponentially [19]. It should be noted that currently TiO_2 is the third most used material as an ingredient of consumer products. Database of Woodrow Wilson shows that in 2011 from a total of 1317 products, 5% contain TiO_2 [20]. The presence of TiO_2 in personal care products were examined in 8 toothpastes and 24 other products [21]. The content of TiO_2 in all tested toothpastes varied from 0.7-5.6 μg/mg, or from <0.1% to approx. 0.5%. The addition of TiO_2 to sunscreens makes them more transparent, with less viscosity and easier dissolvable in skin if compared to ZnO containing products [22].

Food

TiO_2 is commonly used as food supplement [23]. Analysis of 89 foods established that the concentration of TiO_2 is 0,00077 - 210 μg Ti/mg product [21]. As a whole, foods with higher concentration of TiO_2 are pastries, chocolates, gums and foods with white icing and sugar dressing. In some diaries with white color - cheese, milk, yoghurt concentrations of TiO_2 are measured if compared to non-milk substitutes, like drinks based on soya and rice, in which the concentration are 0.10-0.26 μg Ti/ml [20]. Analyzing human exposure to TiO_2 from food, the kids are identified as group of higher exposure. This is mainly due to the highest amount of TiO_2 in pastries if compared to other foods. The typical exposure of grown man from US is around 1 mg Ti/kg human weight/day [21].

Penetration of TiO_2 through the skin

Oral cavity is exposed to TiO_2 when using toothpastes and foods, dental alloys and the atmosphere. Structurally skin and mucosa are similar - build of keratinized stratified squamous epithelium. Despite of this, there are important differences considering the permeability. In the granular and keratinized layers of the oral mucosa lipids, for example (acyl) ceramides are deposited intracellularly aiming to create effective barrier [24]. Oral keratinized epithelium contains 25-50% less (acyl) ceramides if compared to the epidermal layer, which may explain its greater permeability [25]. It is considered that its permeability is 4000 greater than the one of the skin [26]. Nevertheless, the non-keratinized epithelium contains granules, forming amorphous intercellular barrier material, limiting the penetration of bigger molecules, such as toxins, enzymes and pharmaceuticals [24]. Ex vivo experiments with fresh pig buccal mucosa indicate that different size TiO_2 passes through the mucosal layer and penetrates oral epithelium [27].

In the oral cavity unique "junctional" epithelium - stratified squamous non-keratinized epithelium, comprised of two layers - basal and sub-basal, which is highly permeable was established [28]. Cells here are interconnected only by few desmosomes, intercellular spaces are relatively wide, which allows the secretion of liquids and transmission of leukocytes – the first line of peripheral defense against bacteria. During inflammation, epithelium junction may be disrupted because of the increased liquid flow or the action of bacterial or leukocyte products [28]. At a site of tissue inflammation, this epithelium becomes permeable for different materials, from carbon particles to proteins [29, 30].

In vivo, the whole oral epithelium, excluding the junctional one is covered with saliva. Saliva has important cleaning function, and also contains mucins, covalently connected to the surface epithelium. Through the latter sIgA and lysozymes get concentrated, preventing the adhesion of microorganisms. Titanium interacts with the mucous layer very quickly, penetrates the underlying tissue in minutes, and in-

fluences on the physiological homeostasis of buccal/sublingual cells in oral cavity [31]. The hydrophilicity/hydrophobicity of titanium surface influences its distribution in mucosa. The hydrophilic 20 nm TiO_2 Rutile is freely distributed in the cytoplasm, while the hydrophobic become enveloped in the vesicular structures. Although the integrity/viability of cell membrane is not affected, the hydrophilic TiO_2 nano-particles are with higher potential to induce reduction of the mitochondrial membrane physiological potential than the hydrophobic ones, which results in increased production of reactive oxygen radicals [32].

Release of Ti ions from metal alloys in dentistry

Studies were conducted on hypersensitivity reactions to titanium orthopedic implants, but it is unclear to what extent it is possible to extrapolate to those occurring in the oral cavity to dental implants. In dental implants the intraosseous contact surface is less than in orthopedic ones [33, 34], which may be of particular importance considering that bone has a very low reactive potential. On the other hand, oral mucosa and skin are very different from an immunological point of view, partly due to the impact of specific immune mechanisms, such as the association between skin and mucosal lymphoid tissue. Moreover, the contact between metal and the host is difficult because of the fact that the implant and prosthetic structures in oral cavity are coated with a layer of salivary glycoprotein, acting as a protective barrier [35]. Regarding dental implants, several factors in the oral cavity could contribute to release of metals, incl. Ti, if compared to other types of implants. These factors include the constant presence of infection (gingivitis or periodontitis), lipopolysaccharides (constant presence of bacteria), the use of fluoride-containing toothpaste and mouthwash, higher glucose levels, very corrosive environment, including presence of saliva containing corrosive compounds such as hydrogen chloride ions, sulfide compounds, dissolved oxygen and free radicals, with varying pH levels. Corrosion is assisted by both the acidic environment and the presence of lipopolysaccharide [36, 37, 38]. In healthy adults, the salivary pH levels are 6.3 - 7 [36]. Acidic foods, such as soft drinks and fruits, and the presence of infection, reduce saliva pH [39]. Toothpastes not only contribute for the abrasion of metal surfaces, but also contain fluoride, exerting detrimental effect on Ti in high concentrations [40], although data give evidence for corrosion [12, 42, 43, 44].

It is also important to emphasize that mucosa and skin have different specific immune systems, associated with skin and mucosal lymphoid tissue. The number of Langerhans cells in oral mucosa is smaller, and thus it must be exposed to concentrations of allergen 5-12 times greater than those needed to cause tissue reactions in skin [45]. Moreover, in oral mucosa reside various subtypes of immune cells reacting primarily with tolerance in contact with antigens such as lipopolysaccharide [46]. This explains why patients allergic to nickel may still tolerate nickel-containing orthodontic appliances and why oral cavity diseases are relatively rare despite the continuous attack of pathogenic bacteria and other exogenous antigens. In addition, oral exposure to metals such as nickel and cobalt (e.g. when wearing orthodontic brackets) before dermal one result in immune tolerance [47, 48]. Similar considerations are applicable concerning the allergic reactions after implantation.

Titanium concentrations of 100-300 ppm were found in periimplant tissues, often accompanied by discoloration [49, 50, 51]. Evaluation of a skin-sensitizing potential of salts of nickel, chromium, titanium and zirconium carried out. Ikarashi et al. [52] established that significantly higher titanium ions quantities are requires a skin reaction to arise. The amounts of titanium ions released from titanium alloys are considered to be small due to the surface stabilization and corrosion resistance of titanium oxide formed on the surface of titanium alloys. These results may explain the low incidence of contact sensitization to titanium.

Immunology

Four groups of allergens are defined, and one of which includes transition metals. Unlike the classic haptens, metal ions do not form stable covalent protein modifications, but geometrically highly defined coordination complexes, which by definition are reversible and allow the exchange of allergenic metal ions between different binding sites. Due to the latter, it is difficult to identify the metals epitopes.

Like the most common contact sensitizer in industrialized world - nickel, Ti is a transition metal. Data available on the molecular mechanisms of T cell activation by nickel indicate that metal ions, in contrast to classical haptens, are able to activate specific T cells by different mechanisms [53]. The precise mechanism of cause allergic reactions to nickel and Ti is not fully understood yet. The reason why the allergic potential of Ti and Zn if compared with nickel and other transition metals is much lower is also not yet fully understood, despite the actual release of ions in biological fluids. Park et al [18] analyzed the sensitization potential of TiO_2 analyzing the local lymph nodes and established that TiO_2 NPs are not skin sensitizers.

Immune reactions to Ti alloys

Scientific reports indicate that Ti activates macrophages directly or after phagocytosis, and activated macrophages release both pro- and anti-inflammatory cytokines - an imbalance, involved in various pathophysiological processes and allergic reactions. Nakashima et al [54, 55] established that in vitro Ti alloys particles increase the expression of certain chemokines by macrophages in a dose- and time-dependent manner. In a study of Lalor et al [56] investigated tissues obtained from 5 patients with repeat surgical interventions due to unsuccessful hip replacement and established that they were exposed to a big amounts of Ti particles. Histologically, plenty of macrophages and T lymphocytes were found in absence of B-lymphocytes, suggesting sensitization to Ti. In contrast, Flatebø et al [57] treated with Ti dental implants 13 patients without previous implantation. In biopsies obtained 6 months after the treatment, but not in the initial ones, dense particles, most likely metals were observed, but no

tissue sensitivity reactions to the Ti implants were detected. Wang et al. [58] investigated the immune responses and the release of immunoregulatory cytokines after intraperitoneal injection of Ti in mice. The results indicated that the metal-induced immunosuppression may be an important factor for the development of implant-related infection in patients with prosthetics.

Particles released from titanium implants stimulate macrophages more than the ones of other materials used for reconstruction implants [59, 60]. Macrophages release pro-inflammatory cytokines - interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-á) [55], mediating the inflammatory and osteolytic processes involved in periimplantitis [61]. The fact that titanium particles induce inflammation and osteodisintegration among a small part of all implanted patients indicates the important role of individual factors, in particular the immune response to titanium particles [62]. Interleukin-1, TNF-á and anti-IL-1 receptor antagonist (IL1RN) play an important role in inflammatory processes, so that the functional polymorphisms of these genes may be genetically determined risk factors for the failure of implantation. Several studies have associated IL-1 and IL-1RN - polymorphisms with occurrence of periimplantitis [63] implantation failure [64, 65] and peri-implant bone loss [66]. TNF-á is involved in inflammation and bone resorption in experimental model of periodontitis [67]. Multiple TNF-á gene variations in patients with periimplantitis were reported [68].

To develop a diagnostic protocol for individual risk assessment in dentistry is necessary to define a set of markers suitable for predicting the risk of failure after treatment with titanium implants. It is recommended to investigate of the role of genetic variations in four cytokine genes (IL1A 889 C/T, IL1B 3954 C/T, IL1RN 2018 T/C and TNF á 308 G/A), as well as the individual titanium-induced release of cytokines in functional in vitro analysis.

Ti NPs can certainly induce reactions involved in allergic and other inflammatory responses, but the significance of these events and the question of the exposure, especially the dermal one, should be explored further, especially in humans.

Diagnosis of allergies to Ti

The existence and the risk of developing allergy to Ti and TiO_2 are widely discussed [9]. The reason for these discussions is the growing number of reports in scientific literature concerning the adverse reactions to Ti-based alloys and the extremely low frequency of positive reactions in epicutaneous tests to Ti salts, especially TiO_2. The significant increase in use of TiO_2 in personal care products and Ti-based medical and dental implants imposes safety assessment of Ti in terms of its sensitizing potential.

Titanium dental implants are usually well tolerated. The percentage of patients suffering from periimplantitis and with subsequent implant loss is small [69]. When clinical symptoms are obvious, preventive measures are often ineffective. Early intervention or the choice of alternative implant materials with thorough individual risk assessment can improve treatment outcome.

Predicting the risk of treatment failure with titanium implants, the importance of individual characteristics is repeatedly postulated, particularly in relation to genetic features underlying in the individual response to inflammation [70]. Most studies on the genetic basis of implantation failure indicated significant correlations just in cases of combined genetic and non-genetic risk factors. Jansson et al. [64] and Andreiotelli et al. [8] postulated synergy between IL-1 polymorphisms and smoking habits on the incidence of implant loss.

The importance of the individual inflammatory response is further supported by establishment of positive correlation between the production of TNF-á/IL-1â and the failure of treatment with titanium implants. Data from previous studies confirm correlation between the increased production of TNF-á by peripheral blood monocytes and development of related to titanium implant inflammatory arthritis [71]. Titanium particles with a diameter of 1-10 microns penetrating from the implants into the connective tissue are potent stimulators of macrophages, stronger than polyethylene, CoCr, ZrO2 and aluminum particles [59, 60, 72].

Titanium particles were found in tissue macrophages and osteoclasts. Macrophages release IL-1 and TNF-á during the phagocytosis of titanium particles, mediating powerful inflammatory response. Except from the proinflammatory, IL-1 and TNF-á exert osteolytic effects as well. They activate osteoclasts and induce interactions RANK-RANKL, triggering bone resorption [73]. Furthermore, they contribute to the degradation of components of the extracellular matrix by metalloproteinases [74]. In short term, inflammation with moderate release of IL-1 and TNF-á has been shown to favor the primary bone regeneration, a process similar to the osseous integration of dental implants [70]. Low level of inflammation manifestation is a factor favoring the success of implantation because the osseous integration of implants depends on the adequacy of tissue repair [75] and the adequate immune response [76]. The significant or long-term release IL-1 and TNF-á boosts both the inflammatory and the osteolytic processes that result in an increased risk for severe periimplantitis and implantation failure.

Generally, the implant rejection is classified as early, if no osseous integration occur or in case of initial osseous integration, it is disturbed after loading [69, 77]. While the early rejection is associated with systemic diseases, the quantity and quality of bone surgical trauma, and possible contamination during the surgical procedure, the late rejection is more often associated with periimplantitis and biting overload [70]. Due to their inflammatory nature, the latter conditions are influenced by TNF-á and IL-1. Data obtained by Jacobi-Gresser et al. (2013) indicated that both early- and late implant loss is associated with significantly increased production of TNF-á and IL-1â if compared to controls. These data suggest that the individual inflammatory response to titanium particles contribute to increased risk for both early- and late implant loss [78]. This is the first study integrating genetic and functional analysis of IL-1â and TNFá production as diagnostic tool for unsuccessful titanium implants treatment.

The diagnosis of allergy to Ti is usually based on

patient history, clinical findings and the results from patch testing. However, the low epidermal penetration of commercially available Ti salts makes patch testing insufficiently reliable [79, 80]. Examples of some commercially available materials for patch testing are calcium titanate (10% pet.), Ti (III) nitride (5% pet.), TiO_2 (10% pet.), Ti (III) oxalate decahydrate (5% pet.) and Ti (10% pet.) (Available at: www.chemotechnique.se). The presence of impurities (Al, BE, Ni, Cd, Co, Cr, Cu, Fe, Mn, Mo, Pd, and V) in Ti materials resulting from the process of production should be kept in mind when interpreting the results from patch testing. Even the smallest amounts could be enough to trigger allergic reactions among sensitized to the corresponding allergen patients [81].

Currently, is no standard patch test for allergy to titanium and positive reactions are rarely observed in skin patch testing [82]. The sensitivity of patch testing for allergy to metals is about 75%. Some authors suggest that 0.1% and 0.2% solution of titanium sulfate and 0.1% and 0.2% of titanium chloride are successful reagents for epicutaneous testing and could be an alternative to titanium oxide which is commonly used for patch testing [83] but up to date, this method have not been used for the diagnosis of allergy to dental implants.

Quite a few medical doctors use in vitro blood tests for diagnosis of allergy to metals yet. Frequently used are the lymphocyte transformation test (LTT) [80, 84, 85, 86], the test for inhibition of lymphocyte migration [79, 87, 88] and the commercially available memory lymphocyte immune-stimulation assay - MELISA® [89]. Furthermore, flow cytometric analysis is proposed as a method for evaluation of allergy to metal implants [90]. None of these tests have been widely accepted as the optimal method for diagnosis of allergy yet, due to their insufficient validation, cost, difficult access to centers performing such tests, and possible variations in results obtained in different laboratories [91]. Although MELISA® is widely published in vitro assay and a number of publications suggest its clinical application, it is not approved as a routine method for testing allergy to Ti and is still under evaluation.

The sensitivity, specificity and reproducibility of MELISA® for more than 20 different metals, incl. Ti, are analyzed in a study of 250 patients with suspected Type IV allergy to metals [89]. The authors concluded that MELISA® is a reliable method for diagnosis of allergy. However, no studies have been conducted on control groups of healthy individuals. Müller and Valentine-Thon [89, 92] reported about 56 patients with different clinical symptoms after treatment with Ti-based implants. No positive reactions in patch testing were observed. Using MELISA® 37.5% of the reactions were positive with an average stimulation index (SI) 6.3, 28.6% were ambivalent, with a mean SI 2.4, 33.9% were negative (SI<2). Clinical improvement was observed among fifty-four patients after removal of the implant. It should be noted that in this study, 57.9% of patients reacted to other metals, including Ni. These results could be a kind of overestimation of the actual rate due to the considered low specificity of MELISA®. Controls have not been tested. Hallab et al [87] suggested that a system, including a plurality of analysis of various aspects of lymphocyte /monocyte-mediated reactivity could be more useful to improve the accuracy of diagnosis of metal-induced allergy related with implants treatment. The clinical history is essential, especially when allergy to Ti implants is suspected.

In vitro LTT determines the proliferation of lymphocytes after the contact with allergen. Some authors reported false positive results.

Perspectives of diagnosis of sensitization or allergic reactions to titanium

Interleukin-17 (IL-17) and interleukin-22 (IL-22) are produced from a subset of newly defined T-cell line known as Th-17. IL-17 is relates with the pathogenesis of many inflammatory diseases, incl. rheumatoid arthritis and asthma. The number of Th-17 cells and the expression of IL-17 were significantly higher in biopsies in cases with positive patch test results, regardless the nature of the antigen [93, 94, 95]. IL-22 is an important mucosal protection mediator and exerts complex pro- and anti-inflammatory and auto-immune effects. Patients with contact dermatitis to nickel have significantly higher blood levels of IL-22 if compared with the controls [96] - data indicating possible involvement of IL-22 in the pathogenesis of human allergic contact dermatitis.

In 2011, 10 signs were proposed that could serve as indicators for clinically significant allergy to metals in orthopedic implants: (I) chronic dermatitis, manifested weeks to months after implantation; (II) rash overlying the metal implant; (III) morphological characteristics corresponding to dermatitis (erythema, induration, papules, vesicles); (IV) in rare cases, systemic allergic dermatitis (characterized by general reactions, dermatitis, usually localized on body curves); (V) histology consistent picture of allergic contact dermatitis; (VI) positive reaction in patch testing (often strong) to metal in the composition of the implant; (VII) serial dilution patch test gives positive reactions to low concentrations of suspected metal; (VIII) positive in vitro testing results, for example, LTT; (IX) the dermatitis is resistant to treatment; and (X) complete recovery after removal of the implant [97].

No data is available in literature concerning epidemiological studies of the incidence of allergy to Ti in the general population, as no reliable diagnostic test is available.

Clinical responses and case reports

Most of the published data concerns dental and orthopedic implants and cases of contact or systemic hypersensitivity. Cases with suspected allergy to Ti have been described in patients with cardiac pacemakers. Most scientific reports describe manifestation of allergy to Ti as an ingredient of dental and orthopedic materials. The symptoms are different - dermatitis, stomatitis, chronic inflammation in adjacent tissues, difficult wound healing, acne like inflammation of the face, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), chronic fatigue syndrome, muscle and joint pain and neu-

rological problems [92, 98, 99]. It should be noted that several cases are reported of suspected Ti allergy which subsequently was found to be due to other allergens or reasons [81, 99, 100].

While implantation failure in dentistry is often inexplicable and allergy Ti is rarely diagnosed, some authors suggest that this may be just the top of the iceberg [45, 50, 101]. There are reports about children and young people with severe scoliosis and Ti implants, from which a release of big amounts of Ti for many years is possible. Often, patients were re-operated because of pain, rejection of the implant or suspected infection.

No reports in the available literature were found on allergic reactions to Ti as an ingredient of personal care products or to TiO_2 as a whole. However, it is assumed that TiO_2 as an ingredient of cosmetics and sunscreens adsorbs the gold released from jewelry. Therefore, although many patients don't have dermatitis at the site of contact with golden jewelry, TiO_2 can induce jewelry wear and release of fine gold particles that may come into contact with the face and eyelids. In a study regarding eyelids dermatitis high incidence of allergy/positive patch test reactions to gold and interaction with TiO_2 was established, which is the basis to recommend avoiding TiO_2 containing gold jewelry or products, even when patients don't exhibit dermatitis at the place of the primary contact [102].

CONCLUSIONS

1. The exposure of Ti as an ingredient of both implants and consumer products and personal care products is common.

2. It has been proven that the surface of implants made of pure Ti and its alloys release Ti ions, sometimes reaching remote tissues. TiO_2, the most widely used oxide is much more stable than pure Ti and alloys used in the implants, that should be taken into account when conducting research and analyzing the results.

3. The evidences of possible toxic effects are insufficient. It is difficult to assess the frequency of Ti allergy due to the uncertainty of diagnostic methods, but it is believed that it is very low. This is supported by the evidence that Ti and TiO_2 (often as NP) doesn't penetrate through healthy skin.

4. Skin patch testing with currently available formulations of Ti and TiO_2 has no significant value in clinical practice, and currently it is assumed that there is no reliable method for diagnosis Ti allergy.

5. The functional analysis of cytokine release and investigation of genetic characteristics could be useful for individual risk assessment in dental implantology. The overall assessment requires future studies in bigger populations. Such studies may also help to investigate separately early and late implant loss, as well as to develop new diagnostic tools.

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