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Risk Of Titanium Use In Dentistry - A Review Of Literature

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Abstract

Aim-The aim of this article is to provide an overview of the risks associated with titanium materials and to suggest alternative biomaterials as a practical solution.

Introduction-Titanium is considered the material of choice for intra-osseous use in dentistry owing to its excellent biocompatibility, better mechanical properties such as low density, specific gravity and ability to form passive oxide film that provides high resistance to corrosion. With the widespread use of titanium, there have been concerns regarding titanium accumulation and its effects on the human body. The allergic reactions elicited along with the toxicity potential of the particles released due to bio-corrosion have become instrumental in deciding the longevity of the implants.

Review results-The prevalence might be low, but there is enough evidence to suggest thorough history taking and diagnostic assessment for allergies before placing titanium implants in patients. Symptoms of the allergy, soft tissue hyperplastic lesions, peri-implantitis and unexplained implant failures cannot be disregarded.

Conclusion-Clinicians need to be aware of the toxic possibilities that may arise due to titanium use- immediate as well as long term. They should be able to diagnose them, in spite of its rare occurrence. **Clinical significance**- This has paved way for the development of newer non-metal biomaterials to prevent risk of metal associated allergic reactions.

Keywords: Titanium allergy, dental implant, hypersensitivity, corrosion

Introduction

Replacement of the missing teeth using dental implants has become the mainstay of the treatment modality which has substantially increased the quality of life. Numerous biomaterials like metals, polymers and ceramics have long been noted as dental implant biomaterials. The pure titanium, introduced by Branemark during 1960s has prepondered as the dental implant biomaterial owing to its advantages such as the high passivity, ability to repair itself instantaneously if damaged, resistance to chemical attack and modulus of elasticity compatible with that of bone. It has been used since long due to its clinical success. With the widespread use of titanium, though the prevalence of allergic reactions is low there have been concerns regarding titanium ion release, its accumulation and effects in the body.[1-6] The allergic reactions associated with dental implants include skin rash, eczema and allergic contact stomatitis; however, should these allergic reactions be entirely attributed to Ti is controversial. Small consistent amounts of other elements have been detected in Ti alloys which may act as "impurities," that trigger the allergic reactions in patients with Ti implants[7] Secondly, titanium being in contact with biologic systems corrodes [8] and releases ions, which can activate the immune system by forming complexes with native proteins.[9,10] These metal-protein complexes act as haptenic antigens that elicit type I or type IV hypersensitive reactions. [11-13] The data available in the literature indicate that patients having a history of an allergic reaction to metallic devices or metallic jewellery have more propensity to develop a reaction to an implanted device than individuals with no such history. Although titanium is considered to be a biocompatible material but numerous case reports instances of metal sensitivity in the form of skin reactions [14] and potential for adverse human tissue responses to titanium dioxide have been reported.[14,15] The current article provides a general view about the risks associated with titanium materials and suggests alternative biomaterials as a practical solution to circumvent the short comings of metallic biomaterials.

REVIEW RESULTS

Common Symptoms associated with Titanium Allergy In the literature it has been found that he source of titanium ions that may elicit hypersensitive reactions depends upon its various applications from cosmetic to therapeutic uses and dental or orthopaedic implants. The allergic reactions related to titanium that have been observed includes urticaria, eczema, edema, redness and pruritus of the skin or mucosa, either localized, at distant sites, or generalized, allergic contact stomatitis to impaired healing of fractures.[3,16-18] Egusa et al demonstrated the emergence of facial eczema in association with a titanium dental implant placed for a mandibular overdenture supported by 2 implants in a clinical case. Symptoms relieved by the removal of the titanium material.[1]In their review, Siddiqi et al suggested that titanium can induce hypersensitivity in susceptible patients, and could play a critical part in implant failure.[19] In some patients, Yellow nail syndrome has been diagnosed after eating TiO2-containing medication such as diclofenac, celecoxib, and zopiklon, along with gum, candy, and licorice. In such cases, symptoms were improved when drug usage was discontinued.[20,21] Yellow nail syndrome was first designated as a medical term by Samman and White during their report of a patient with nails growing slowly, thicker, and yellowish in color in conjunction with lymphedema syndrome. In 2011, Berglund and Carlmark evaluated 30 patients with yellow nail syndrome via energy-dispersive X-ray fluorescence (EDXRF) and found titanium ions as a pathogen of yellow nail syndrome.[22-24]

Causes of Allergy related to Titanium and Titanium alloys

Titanium is considered as a bioinert material and is demonstrated to have low toxicity and is well tolerated by the human body. The adult body contains between 1.5 to 11 ppm of the metal, spleen and adrenals being the prominent storage organs. Hypersensitivity reaction to a metal (ionic form) comes following ingestion, skin or mucosal contact, or from implant corrosion processes. In their ionic form, metals can be bonded with native proteins to form haptenic antigens, or can trigger the degranulation of mastocytes and basophiles, being capable of developing type I or type IV hypersensitive reactions according to Schramm and Pitto.[5] Occasionally, titanium-bearing dusts behave as mild pulmonary irritants, although such incidents are far less significant when compared with many other inhaled particles in accordance with the literature evidence.[25,26]Rae et al [27] has reported the effects of metal particles on cells. This study showed that while nickel, cobalt-chromium alloy and especially cobalt were all toxic, titanium, along with molybdenum and chromium, showed no effect. There are some causative factors listed below related to titanium ions release and titanium allergy:

Presence of Impurities Titanium also exists in the form of various alloys such as sponge titanium, TiAl6Nb7, TiAl6V4 [forged alloy], TiAl6V4 [cast alloy], TMZF (Ti-12Mo-6Zr-2Fe), pure titanium and iodide titanium which have been analyzed for the presence of the minor elements that are associated with allergic reactions using spectral analysis. It has been investigated that these small amounts may be sufficient to trigger allergic reactions in patients suffering from the corresponding allergies, such as a nickel, palladium or chrome allergy. However, these allergic reactions would not be directly attributable to titanium or its alloys, but rather to the impurities contained therein which have also been found to be associated with the hypersensitive reactions.[7] Rogers et al tested the toxicity of vanadium and niobium in titanium alloys and found that human monocytes released more inflammatory mediators around metal debris due to Ti-Al-V compared to titanium-aluminum-niobium (Ti-Al-Nb). At the end of study, the authors also suggested that metal debris particles might lead to bone loss around the prosthesis.[28]

Effect of Corrosion

Titanium is highly reactive to oxygen, therefore, cannot exist freely in its cationic form and results in titanium oxide layer (TiO2) formation that provides passivation. This oxide layer can be disrupted mechanically or biologically due to various factors, and such damages can result in the release of titanium particles. Mechanical wear of implant surfaces can occur at different instances such as during implant placement, during the fitting of a dental prosthesis, during mechanical cleaning for the prevention and therapy of peri-implant infections.Dental implants are exposed to an environment containing large amounts of microorganisms which may result in the development of adherent bacterial biofilms on all implant surfaces. As these biofilms develop, the bacteria modify their environmental conditions, notably with regard to pH and the concentration of oxygen, and promote inflammatory reactions in adjacent host tissues.[29] Bacteria play a prominent role in the initiation of corrosion. The effect of early colonization of planktonic bacteria on titanium surfaces of implants has been investigated.[30] Both of these phenomenon lead to **"Tribocorrosion"** that is a material degradation process due to the combined effect of friction/wear and corrosion.[31]Titanium particles and their degradation products have been detected in oral and non-oral tissues, the origin of which remains controversial. In subjects with dental implants, their origin can be easily traced to the metallic device. Titanium implants may corrode and release ions or micro-particles which can induce inflammation in affected tissues. This mechanism has been suggested to play a role in the loosening of implants. [32] Animal studies have demonstrated traces of titanium after implant placement in tissue specimens of lungs, kidneys, and liver that were disseminated throughout the body via the bloodstream by plasma proteins or phagocytic cells to specific organs like lungs, spleen, liver, or abdominal lymph nodes. However, these studies have also shown that particles originating from a non-dental source can accumulate in the gingival tissues. [33]

Effect of Fluoride Concentration and pH on Corrosion Behaviour of Titanium

Nakagawa et al studied the effects of fluoride concentration and pH on the corrosion behaviour of Ti and conducted anodic polarization and immersion tests in NaF (sodium fluoride) solution of various concentrations and pH values. In this study, it was found that the corrosion of Ti in the solution containing fluoride depended on the concentration of hydrofluoric acid (HF). The passivated Ti oxide film was destroyed on increasing the concentration of HF above 30 ppm.[34] Barao Valentim et al studied that the pH level of artificial saliva influences the corrosion behaviour of cp-Ti and Ti6Al-4V alloy in that lower pH accelerates the corrosion rate and kinetics.[35] In another study, the electrochemical corrosion behaviour of Ti-1M (M = Ag, Au, Pd, Pt) alloys together with the currently used Ti-6Al-7Nb alloy metallic biomaterial were investigated for dental applications by Rosalbino et al. The overall electrochemical data indicate a positive influence of noble metal alloying additions, especially gold, on the corrosion behaviour of titanium. This could be ascribed to a strengthening of the passive oxide film due to the possible incorporation of noble metal cations into TiO2 lattice, thus increasing its dissolution resistance.[36]

Galvanic corrosion

In many studies, the main source of titanium ions release was reported to be due to corrosion caused by galvanic effects between titanium implants and gold and/or amalgam restorations and corrosion due to fluorine oxidation. [21]

TiO2-containing medication

In some patients, titanium dioxide used in drug coatings such as diclofenac, celecoxib, and zopiklon was considered to be the source of titanium ions. [20,21]

Release of Titanium ions due to mechanical wear of implant surfaces Mechanical wear of implant surfaces can occur at different instances: during implant placement, during implant –abutment connection and the fitting of a dental prosthesis, due to mechanical cleaning in treatment of periimplantitis, and as a result of micromovements of parts of the implant and the suprastructure during function. Five months after insertion, the Ti particles were not found in the bone at the implant site, but were found in high levels in the lungs as compared

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with other inner organs.Schliephake et al showed with scanning electron microscopy (SEM) in an animal study (mini-pigs) that Ti particles were abraded from Ti fixtures and screw taps and were found in the adjacent bone. Meyer et al used SEM to investigate bone from peri-implant sites after insertion of implants with varying surface roughness; they found the highest levels of Ti at sites with Ti plasma sprayed implants. Total bone-implant area and diameter of the drilled implant site seem to be of less importance when compared to surface roughness regarding amount of Ti released from the implant. The reasons behind this, first, rougher implant surface induce more friction during insertion, which could lead to particle detachment from the implant. Second, variation in surface roughness affects the coefficient of friction, which gives a higher insertion torque for the implant during insertion. The release of Ti during installation of an implant may be a factor of importance for the inflammatory process in peri-implant tissue.[37]

Histological Studies of the Bone Adjacent to Titanium

In previous years, many histological studies have been done to investigate the reactions occurring at cellular level related to release of titanium ions. No allergic reaction was found in various studies except 'Metalosis' (deposition of metal ions in the adjacent bone and soft tissues around the titanium bone screws or miniplates). (Table-1)

Table-1: Histological studies of the bone adjacent to Titanium

Author	Study	Result
Hirai et al[38]	Studied the bone histologically adjacent to titanium bone screws used for mandibular fracture treatment using the Levai Laczko and toludine blue methods.	Black particles were observed in the bone and soft tissues around the titanium bone screws. Multinuclear giant cells resembling macrophages were observed near these particles. No evidence of allergic reaction was found.
Thewes et al[39]	Analyzed the cells of perivascular infiltration in the tissues adjacent to titanium (n = 23) and steel (n = 8) orthopaedic implants after explantation of the metals by immunohistochemical methods. Metallic orthopaedic implants are composed of elements that are known to be skin sensitizers in the general population. The following panel of monoclonal antibodies were used as parameters: CD 1a (Langerhans cells), CD 4 (T-helper cells), CD 8 (T-suppressor cells), CD 11c (monocytes and macrophages), CD 45 RO (memory cells), CD 45 RA (naive cells), eosinophil cationic proteins (ECP), neutrophil elastase, and human leukocyte antigen –DR isotype (HLA-DR).	The number of perivascular total cells did not differ significantly. They concluded that sensitization to metals is possible in the tissue adjacent to steel and titanium implants, because all cells which play an important role in allergic delayed-type hypersensitivity (type IV) reactions are present. This phenomenon may be called a 'pre-sensitization' phase, because no sensitization or allergic reactions were seen in their cases.

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Katou et al[40]	Studied the immuno-inflammatory responses to titanium miniplates used in the treatment of mandibular fractures immunohistochemically at light and electron microscope levels using haematoxylin and eosin stains.	All specimens were composed of fibrous connective tissue in which metal particles appeared to varying degrees, from tiny black spheres to aggregated large opaque granules. Some macrophage-like cells had phagocytozed fine metal particles. The clinical relevance of this observation is that the removal of non-functioning plates and screws after healing is deemed necessary, particularly in young people.
Flatebo Rigmor S.et al[15]	In this study, thirteen patients, 21 to 69 years of age, without previous implants were included. Prior to wound closure after implant placement, a full mucosal tissue slice was biopsied from the edge of the mucoperiosteal flap (baseline). Second biopsy was taken after 6 months in which tissue reactions were analyzed by coded histometric analysis.	Tissue sensitivity reactions to titanium implants were not disclosed in this study. All 6-month biopsies contained dense particles that were most likely metals.
Torgersen et al[41]	In this study, subepithelial soft tissue and bone obtained from the implant bed in the vicinity of stainless steel and titanium miniplates and screws were evaluated with respect to the presence of immunocompetent cells. The ABC (avidin-biotin-complexjimmunoperoxidase staining technique using monoclonal antibodies defining T lymphocytes ($CD3^+$ macrophages (CDlIc+) and Class II MHC (HLA-DR) was performed on EDTA demineralized, frozen bone tissue, and on fresh frozen soft tissue specimens.	The results showed scattered T lymphocyte clusters, small numbers of macrophages and abundant expression of HLA-DR in the soft tissue adjacent to both stainless steel and titanium implants. No substantial difference was seen in tissue reactions between implants of the two materials. Mild tissue reaction was seen in the vicinity of miniplates and screws of stainless steel and titanium. They concluded that the intensity of the reaction indicates that the implants are well tolerated by the host tissue.

Diagnostic tests for titanium allergy

Today various diagnostic tests are available to check titanium allergy these include Patch test, Memory lymphocyte immuno-stimulation assay test (MELISA), Lymphocyte transformation test (LTT) and blood tests. [42] Thomas et al[3] reported eczema symptoms and improper bone formation in the case of a 35-year-old male patient with a titanium implant in the fracture of his hand using patch test. In this case, the patch test showed a negative reaction to

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titanium, nickel, chromium, cobalt, etc. However, the lymphocyte transformation test showed an increased pattern for titanium. Lalor et al[43] also reported hypersensitivity reactions to titanium and reported the proliferation of inflammatory cells in patients with failed orthopedic prostheses.

DISCUSSION

Titanium is the ninth most found element. It was isolated in the rutile mineral form (TiO_2) by the German chemist Heinrich Klaproth. However, only in 1887, the impure metallic titanium was produced and in 1938, Justin Kroll developed a method of producing commercial titanium through the reduction of titanium tetrachloride ($TiCl_4$) with magnesium at 800 C in argon atmosphere (Kroll Process). By this process porous product known as titanium sponge is obtained which, subsequently, is purified to reach the commercial product.[44]Titanium can be found in different combinations for use in dentistry. Pure titanium is composed by 99.5 % of titanium and 0.5 % of interstitial elements (carbon, oxygen, nitrogen, hydrogen and iron). The ASTM (American Society of Testing and Materials) Standard classified titanium in different grades according to its purity, which is evaluated according to the amount of oxygen. The titanium melted only from titanium sponge is known as titanium grade 1 (the most pure grade). When titanium sponge is mixed with titanium fragments (the amount of oxygen (O_2) and iron (Fe) increases), titanium becomes harder (titanium grades 2, 3 and 4). Therefore, grade 1–4 refers to cp-Ti. Grade 5 refers to the three combinations of titanium (Ti), aluminum (Al) and vanadium (V). The toxicity related to titanium and titanium alloys have already discussed in this review.[7,28,44, 45]With the widespread use of titanium, there are concerns regarding the adverse effects of titanium accumulation and its effects on the human body. With the use of titanium implant, a stable titanium oxide film (1.5–10 nm thickness) is spontaneously formed at the implant surface when its surface is exposed to air. Once the oxide layer is formed (passivation), it provides resistance to corrosion. This oxide layer can be damaged by various environmental and functional factors (abnormal cyclic loads, micromovement of the implant and implant-abutment interface, acidic environments and the combined effects of these factors). In the event of damage, it can spontaneously reform under normal physiological conditions (re-passivation) but continued attack of the implant surface by these factors can result in permanent damage of the oxide film. Further varying pH conditions can turn the implant environment into a more acidic environment and active dissolution of metallic ions can occur (corrosion). These released ions may cause hypersensitive reactions.[45]It has been seen that particulate debris produced from wear and corrosion of implant generally ranges from 0.01 to 100 µm. Debris bioreactivity can be both local and systemic. Local inflammation is primarily mediated by local immune cells called macrophages, which produce pro-inflammatory mediators/cytokines TNFα, IL-1β, IL-6, and PGE2. Although there are many concerns associated with systemic reactivity to implant-debris, to date well-established systemic reactivity has been limited to developed hypersensitivity/allergy reactions.[46]According to the literature, the prevalence of allergy-positive reactions against titanium is far lower than that of other materials such as chromium, mercury, palladium and nickel. In retrospective study, Kitagawa Masae et al [47] analyzed the results of allergy to titanium and assessed its current status. Various types of metal reagents were used for patch testing to detect different metal ions including Ti reagents (either 0.1% Ti sulfate, Ti chloride or Ti oxide). The results of this study revealed a high prevalence of allergy to Pd and Zn, and also revealed the existence of Ti-positive patients.Metals in the oral cavity are ionized and at risk for inducing allergies depending upon their concentration. Various histological studies related to titanium use showed metalosis and no evidence of allergic reactions.[15,39]However, some clinical studies evidence the allergic symptoms related to titanium such as rash, urticaria, pruritus, swelling in the orofacial region, oral or facial erythema, eczematous lesions of the cheeks, or hyperplastic lesions of soft tissue (the peri-implant mucosa) (Mitchel et al, 1990).

Why dental implants rarely show allergic reactions??

According to the literature, it varies based upon patient's immune response. Patients with a previous history of allergies to metallic devices or metallic jewellery are more prone to develop allergic reactions to dental implant. The need for long-term clinical and radiographic follow-up of all implant patients who are sensitive to metals is also required. Other

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reasons include smaller intraosseus contact surface in dental implants than orthopedic ones, which may be particularly important considering that bone has a very low reactivity potential. Moreover, contact between the metal and the host is hampered, as the implant and prosthetic structures in the oral cavity are coated with a layer of salivary glycoprotein, which act as a protective barrier. [42, 48-50]

When to do diagnostic tests??

Before implant placement- It has been shown that people with a history of allergy to metals or jewellery have a greater risk of developing a hypersensitivity reaction to a metal implant (Hallab et al, 2001).[51] Therefore, there is need ofallergytesting before implantation **After implant placement**-The failure of implants has been widely studied, and the infection and overload are main causes of dental implant failure (Esposito et al, 1999a, 1999b, 1999c). However, some failures are difficult to explain, such as spontaneous rapid exfoliation of the implant without any infection or overload risk factor identified. Authors agree that in these cases, there must be a systemic determinant of failure that has not been identified or understood. An allergic reaction can be reasonably suspected after dental implant placement, on the basis of signs or symptoms associated with allergy. In these cases, allergy testing should be performed. [52-55]

Future prospects for Diagnosis of Titanium Allergy

Interleukin-17 and Interleukin-22 are produced by a subset of a recently defined T–cell line, known as Th-17. Both have a role in anti-inflammatory and autoimmune reactions. It would be interesting to develop a blood test, based on the measurement of the production of IL-17 and/or IL-22 by lymphocytes, in order to be able to diagnose with certainty a sensitization to titanium. The research is going on to develop a technique, using flow cytometry, for the purpose of detecting the activation of lymphocytes stimulated by a metal, and measuring different inflammatory mediators released in response to the metal. [52]

Role of Surface Modifications

Titanium ions release due to corrosion can be decreased using surface treatments one of them is nitration, which involves introducing nitrogen in the first micrometer of the surface to promote the formation of TiN and increase corrosion resistance.[56] However in one of the clinical report, a patient treated with an implant and fixed dental prosthesis for the mandibular arch developed contact stomatitis due to a TiN-coated implant abutment. After its removal and the placement of an uncoated abutment, the contact stomatitis healed. This clinical report suggests an allergic reaction to the TiN-coated dental implant abutment in this patient. Although patients with a TiN allergy are rare, such a reaction to the TiN-coated abutments used in clinical dentistry needs to be further discussed and investigated. [57]

Other surface modification processes which can be employed to improve the corrosion behavior and other desirable properties of bio-grade Ti are: physical and chemical vapor deposition, laser cladding, thermal oxidation and thermal spraying, plasma spray, ion implantation, micro-arc oxidation, sandblasting and electrochemical treatment.[56]

Alternative Biomaterials

In the view of titanium allergy, researches are going on to find out the alternative substitutes or methods to overcome the allergic problems. Magnesium (Mg) has recently been in the focus of scientific interest due to its favourable effect on the process of osseointegration. As the essential macro element of the human body, Mg participates in important intracellular energy processes and stimulates the differentiation of pluripotent cells, proliferation and migration of osteoblasts.

In an in-vitro study, it has been seen that addition of fluoride (F) in Modified Fusayama's artificial saliva (AS) increases the amount of released Ti ions with a presumption of F as a very aggressive and reactive halogen that can destroy the protective dioxide film. In this study, an innovative experimental material Ti with Mg was used that results in low release of Ti ions when compared to CP-Ti that shows that the Ti-Mg materials have high corrosion resistance.[58] Rosalbino et al, in an electrochemical study, demonstrated better corrosion resistance of titanium by adding noble metals to it.[59] Fojt et al, in the study with Ti-39Nb alloy, reported that the process of powder metallurgy and consequent porosity could be the reason for better corrosion resistance of such materials.[60] Recently, CAD/ CAM materials have become widespread in dental treatment, and the use of non-metallic materials like polyether ether ketone (PEEK) is going on.[61] In the future, demand for dental treatment using low ionizing materials, such as zirconia and ceramics, will increase.[62,63] However, long term clinical studies are required for evaluating their success and effective use in dentistry.

CONCLUSION

Additional research on the release of the titanium alloy components and alternative methods should be evaluated to produce pure titanium and titanium alloys containing fewer impurities, for use in the human body. The complete mechanism of allergic and/or hypersensitivity reaction with metal materials is not known; the total amount of exposure to specific metallic ions is an important parameter. The extent of exposure to titanium based materials in everyday life and medical applications is increasing, so the number of the titanium-allergic patients will probably increase in the near future. Therefore, history of hypersensitivity reactions to metals should be taken before implantation, and testing for allergic reactions should be recommended to patients who have experienced such reactions.

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