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Allergic Reactions Due to Titanium in Dental Implants

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***Abstract*: Titanium biomaterials have become an indispensable part of medical application, especially in dentistry in the form of dental implants and superstructure due to its corrosion resistance biocompatibility and osseointegration properties. Titanium and its alloys, mainly vanadium, aluminium, titanium are used in the manufacture of implants, hybrid prosthesis and metal frameworks. As a result of its improved physical properties, titanium and its alloys are used in medical applications. However, recently some studies have reported allergic reactions due to titanium implants. Titanium undergoes tribocorrosion in the oral cavity that leads to release of titanium ions in the surrounding tissues and its accumulation manifests as allergic reactions such as allergic contact stomatitis.**

***Keywords*: Titanium, allergy, implants, tribocorrosion.**

1. Introduction

Titanium biomaterials has revolutionized clinical oral implantology, making titanium the implant material of choice currently [1]. Titanium (Ti) is known for its high resistance to flexion and corrosion. Since the second half of the twentieth century, it has been used in many different fields; such as military purposes, aerospace, sports equipment, jewelry, etc. In the field of medicine, it is used to fabricate pacemakers, implants, and stents. From the earliest days of implant dentistry, titanium has been considered the gold standard material for fabricating dental implants due to its excellent biocompatibility, strength, and osseointegration capacity, the key factor required for long-term implant stability. Titanium is used as either pure metal, or in alloyed form in various aerospace applications, and in medical and dental. It is generally alloyed with metals such as Vanadium (V) and Aluminum (Al) forming light-weight yet strong alloy for the fabrication of implants or framework for fixed dental prosthesis.

Implants are the alternate treatment of choice for replacing missing teeth. The requirements of implant materials encompass biocompatibility, acceptable stability in the long term, acceptable function and ease of manufacture [2]. Biocompatibility and stability are closely related in that some materials are known to encourage bone growth which results in a very intimate interface between the bone and implant thus stabilizing the latter. The discovery that titanium alloys predictably promote long term osseointegration by Swedish orthopaedic surgeon Branemark revolutionized the use of endosseous implants in dentistry. Titanium alloys commonly used today are commercially pure (cp) titanium and titanium alloy. Commercially pure titanium is an alloy of approximately 99 wt% titanium and small amounts of oxygen and traces of iron, carbon, hydrogen, and nitrogen. The amount of oxygen determines the grade of the alloy, with oxygen concentrations of 0.18 wt% used in grade

I alloys and 0.40% in grade IV alloys. Increasing amounts of oxygen increase the strength and decrease the ductility of these alloys, leaving the modulus of elasticity, density, and melting range affecting the phase structure, and corrosion resistance of these alloys. Titanium alloys of interest include Ti-30Pd, Ti-20Cu, Ti-15V, and Ti-6Al-4V. Titanium alloy applies to an alloy similar to commercially pure titanium but with 6 wt% aluminum and 4 wt% vanadium. The addition of aluminum and vanadium doubles the tensile strength of this alloy relative to grade 4 titanium but also reduces its ductility [3]. Titanium alloy also osseo integrates with bone, but with minor differences in the character of the bone around the implant. Titanium’s unyielding nature against electrochemical degradation; benign biological reaction; relatively light weight; and low density, low modulus, and high strength make titanium-based materials suitable for use in dentistry. Titanium has been called the "material of choice" in dentistry because of its strength and the minimal biological response it elicits. The strength of titanium is attributed to its hexagonal tightly packed crystal lattice and macromolecular orientation, whereas its corrosion resistance is credited to its stable, passive oxide layer.

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Titanium based materials are well accepted by the body because of their passive oxide layers. The major as well as the minor alloying constituents can be tolerated by the body in traces. The commercially pure titanium or titanium alloy surface is covered with a complex mixture of adherent titanium oxides. Many types of oxides are present at the surface of titanium, and they are responsible for the osseointegrative properties of these alloys. The thickness of the oxide layer varies from 20 to 100 Å, with oxides rich in oxygen closer to the surface and those poor in oxygen nearer the alloy. Titanium alloys re-form these oxides immediately after any damage to the alloy surface because titanium is too reactive to exist in unoxidized form in an aerobic atmosphere. The corrosion resistance of commercially pure titanium or titanium alloy in bone, soft tissues, or oral cavity is a great asset from biologic and restorative point of view. However, recent studies have reported cases of allergic symptoms caused by titanium based materials in dentistry. An allergic reaction, or hypersensitization, is an excessive immune reaction that is elicited on contact with a known antigen. Titanium to evoke an allergic reaction, must have antigenic characterization and stay in contact with the organism. The placement of titanium implants and their existence in the human body intensifies the amount of internal exposure and it is proven that titanium ions accumulate in tissues surrounding dental and orthopedic implants, regional lymph nodes and pulmonary tissue [4]. Ionic concentration between 100 and 300 ppm have been reported in peri-implant tissues, along with discoloration. The usage of titanium in products has increased with advances in smelting technology, thus providing more chances for humans to be sensitized to this metal. Hypersensitivity to medical or dental titanium implants, is indicated by a transitory coalition between exposure to titanium and occurrence of tissue reaction proximal to implanted titanium. In the oral cavity, titanium implant-associated allergic reactions usually manifested as type IV hypersensitivity reactions [5].

2. Mechanism of Titanium Degradation

Oral reconstruction devices are sensitive to bio-tribocorrosion phenomena in the oral environment due to the synergism of wear, chemical, biochemical, and microbiological processes. The titanium (Ti) properties such as structural material, connection design, surface treatments, and alloying elements influences the material behavior. In addition, wear-corrosion factors such as cyclic loads, micro movements, oral biofilm, and decontamination methods are also related to dental implants degradation. These environmental conditions to which dental implants are exposed leads to the release of Ti particles and ions with cytotoxic and harmful effects on periimplant surrounding tissues [6]. The combined effects of the interaction between wear and corrosion on the surface of a material is known as “tribocorrosion”. In short, it is a science that studies the correlation of wear, chemical, and electrochemical processes. Tribocorrosion can be defined as a material degradation process of surfaces (wear, cracking, corrosion, etc.) subjected to the combined action of mechanical loading (friction, abrasion, erosion, etc.) and corrosion attack caused by the environment (chemical and/or electrochemical interaction).

The fundamental test system used to interpret the tribocorrosion process in the oral environment to the worktable includes electrochemical and tribological synergic analysis. The mechanical (load applied, frequency, stroke distance, and number of cycles) and electrochemical (solution composition, anion concentration, and pH) test conditions are factors used to evaluate material’s tribocorrosion performance [7]. To prevent the occurrence of tribocorrosion process some modifications have been done such as proper material selection, alloying elements for Ti-alloys manufacture, surface treatments, and biomolecules immobilization. The degeneration products generated by tribocorrosion process impacts the success of dental implants due to Ti-based wear, cracks generation, particles and ions release. These implant degeneration products can stimulate unfavorable biological responses such as susceptibility to peri-implant infection and progressive bone loss. Therefore, such deleterious effects impact the implant life and increase the chances of failure. The tribolayer is a mixture of organic constituents from oral fluids and metal particles present on the surface interface. The stability and thickness of tribolayers are modified in a nanometer scale according to wear and corrosion degradation conditions. Tribolayers are formed as a result of the physico-chemical interactions of surfaces under relative motion with mutual transfer of materials between surfaces[8]. The presence of tribolayers are beneficial for implant surface properties, since it can exert a corrosion protection. However, during the bio-tribocorrosion process the tribological forces applied on the surface can affect tribolayer stability and lead to tribofilm removal. In this way, the tribolayer of Ti-based implants are commonly subjected to damages by tribocorrosion phenomena since the placement of implants. Firstly, material loss can occur during the implantation when friction forces are applied to implants exposed to body fluids. The insertion torque, loading, and implant replacement cause friction at the bone/implant interface which may be responsible for the release of metallic wear debris causing modifications to the surface and implants geometry [9]. During chewing, physiological cyclic loads can create micro movements and consequently micro-gaps between implant-abutment and abutment-prosthetic crown. These micro movements induce the metal wear particle and ions release that is not entirely bioinert materials. The micro-gaps increase the contact of saliva and oral biofilm with implant surfaces exacerbating the corrosive process. Additionally, the characteristics of implant systems such as structural material, connection design, and surface treatments also influence the related tribocorrosion damages. Furthermore thermal, ionic, enzymatic, and microbiologic factors of the oral environment increase the corrosive behavior and electrochemical degradation of dental implants. Specifically, saliva influences the tribocorrosion process as it is a complex mix of fluids of several inorganic and organic compounds. Lower pH conditions promote the degradation of Ti surface due to the reduction of corrosion resistance. In general, acidic environment favors the ions exchange between the implant surface and saliva, inducing higher corrosion rates. After implant placement in the oral cavity, the salivary pellicle starts forming immediately onto dental implants surfaces. Consequently, implant surface is soon colonized by oral bacteria forming biofilms. And acidic metabolites produced by the bacteria are related tend to increase the corrosion of Ti material. Thus the higher corrosion of Ti due to bacteria and inflammatory reaction products can increase the surface roughness, favor microbial attachment, and further influence the bio-tribocorrosion of Ti material [10]. Concerning chemical and mechanical degradation, there is no consensus in the literature regarding the most important factor for the tribological behavior. It is related to the rate of material degradation that is not predicted by the wear or corrosion behavior separately, but rather by the synergistic effect of both factors. Corrosion can further increase Ti dissolution particles and affect the structure and composition of the submucosal microbiome, inducing higher rates of inflammatory response. Additionally, material degradation can, increase crestal bone resorption and also increase the possibilities for higher amplitude of micro-movement and implant failure. Mechanical methods may cause irreversible structural destruction in dental implants (e.g., polishing, finishing, and implantoplasty) while chemical methods (e.g., chlorhexidine, citric acid, H2O2) are more related to damage of the TiO2 layer and electrochemical corrosion of the Ti surface[11]. Therefore, the impact of bio-tribocorrosion in the oral environment is directly related to the rupture of the TiO2 layer through the complex oral factors (e.g., cyclic loads, micro movements, saliva acidification, oral biofilm, and decontamination methods) with consequent loss of wear debris (e.g., particles and ions release) which leads to constant degradation of dental implants structure.

3. Allergic Reactions due to Titanium

Several studies have reported allergic reactions due to titanium. Allergies to titanium are uncommon but represent a real possibility that should not be overlooked in patients requiring prosthodontic rehabilitation with dental implants. Allergy can trigger a range of symptoms. Patients who have already been diagnosed with allergies to other metals will be more predisposed to titanium allergy. In their ionic form, metals can be bonded with native proteins to form haptenic antigens, or can trigger the degranulation of mastocytes and basophils, being capable of developing type I or type IV hypersensitive reactions. Sensitivity to titanium is characterized by the local presence of abundant macrophages and T lymphocytes and the absence of B lymphocytes, indicating Type 4 hypersensitivity. Ali Robaian Alqahtani et al [12] reported a case of acute allergic reaction to a titanium implant placed in the maxillary premolar area where the patient had a history of metal allergy complained of hypersensitivity reaction such as pain, eczema, swelling, burning sensation, erythema of the oral mucosa around the surgical site with purpuric patches on the palate along with few mouth ulcers. Hyun-Pil Lim et al [13] reported a case of allergic contact stomatitis due to hypersensitivity to TiN-coated abutments in an elderly patient three months after implant placement. Allergic contact stomatitis is an oral mucosal immune inflammatory disorder characterized by erythematous plaques, vesiculation, ulceration, and/or hyperkeratosis and by pain, burning sensation, or itchiness. It is brought about by a T cell-mediated, delayed hypersensitivity immune reaction generated by a second or subsequent contact exposure of an allergen with the oral mucosa, in a genetically susceptible, sensitized subject. Maki Hosoki et al [14] reported the case of a patient who received two dental implants in the right mandible presented eczema that disappeared following the removal of dental implants. LA du Preez et al [15] reported a case of patient in whom six endosteal implants of the same grade IV titanium were placed in the anterior mandible, showed swelling in the submental region and labial sulcus, pain, hyperaemia of the surrounding soft tissues. Hiroshi Egusa et al [16] presented a case of a patient with inflammatory skin lesions on face typical of eczema where 2 years earlier, the patient had received 2 dental implants made of ASTM grade I high-purity titanium in the mandible. Kurt Muller, Elizabeth Valentine-Thon [17] studied the findings of fifty-six patients who had received titanium-based implants and developed clinical symptoms such as dermatitis and acne-like facial inflammation.

4. Clinical Manifestations of Allergy to Titanium

Numerous studies have reported various clinical manifestations in patients due to allergic reaction to titanium including episodes of hives, eczema, edema, reddening, and itching of the skin or mucosa, which may be localized, or generalized. They have also been associated with atopic dermatitis, disturbed fracture healing, pain, necrosis, and weakening of orthopedic implants. In the field of implant dentistry, clinical manifestations include the appearance of facial erythema, disseminated facial eczema, contact dermatosis, atopic eczema, bullous eruptions, and proliferative hyperplasia tissue, edematous tissue, or non-keratinized tissue. Patients with oral allergy demonstrate various clinical features such as burning or tingling sensations, generally associated with swelling, oral dryness, or loss of taste, or occasionally more common signs and symptoms (headache, dyspepsia, asthenia, arthralgia, myalgia)[18]. Allergy in the oral cavity manifests as erythema of the oral mucosa, labial edema, or purpuric patches on the palate, mouth ulcers, hyperplastic gingivitis, depapillation on the tongue, angular cheilitis, perioral eczematous eruption, or lichenoid reactions. Type I allergy may appear clinically in the orofacial region, in the acute form as swelling, may involve the upper respiratory tract, and be dangerous for the patient. In serious conditions, it may convert to urticarial reactions with or without tingling sensations confined to a small area in the oral or pharyngeal cavity.

5. Diagnostic Tests

Various diagnostic tests are available to assess allergies to metals in general and titanium in particular. In epicutaneous patch testing (in vivo), substances located on the back or forearm are evaluated over a 3–7-day period. The epicutaneous patch test is one of the most common and important tests for metal allergy. Patch test reactions are interpreted by using criteria similar to International Contact Dermatitis Research

Group (ICDRG) criteria: negative reaction, doubtful reaction (erythema only, no infiltration), weak positive reaction (erythema, infiltration, possibly discrete papules), strong positive reaction (erythema, infiltration, vesicles, papules), extreme positive reaction (erythema, infiltration, confluent vesicles), and irritant reaction[19]. However, because of the skin's qualities of sealing and protection against direct contact, the test is not very sensitive, may give a false positive or negative, and only detects some 75% of Type IV metal allergies. Lack of standardization may limit the use of a patch test. Nevertheless, it is the most widely used test despite the fact that it is not completely accepted to be the most effective. In the cutaneous injection test (in vivo), the allergen is injected intradermally in the forearm. Red papules and vesicles are considered to show a positive result. This test is only recommended for Type I allergies and not for oral allergies. The lymphocyte transformation test (LTT) is applied in vitro for mucosa-sensitizing allergens. Both local and systemic effects can be analyzed with this test. The MELISA test (Memory Lymphocyte Immuno-Stimulation Assay) is a modification of the LTT (in vitro), which analyzes both local and systemic effects.

6. Discussion

Investigations have been carried out about hypersensitivity reactions with titanium orthopedic implants; but very few have are being carried out in relation to dental implants. The intraosseus contact surface is smaller in dental implants than in orthopedic ones, which may be significant considering that bone has a very low reactivity potential. Moreover, oral mucosa and the skin react differently from an immunological perspective, partly because of the influence of specific immune systems for each organ, such as skin associated lymphoid tissue and mucosa-associated lymphoid tissue. A practical application is that, in mucosa, the number of Langerhans' cells, which act as antigen-presenting cells, is much smaller. Due to its reduced permeability, oral mucosa must be exposed to allergen concentrations 5-12 times greater than the skin in order to cause tissue microscopic reactions. 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[20]. It is important to recognize the difference between the presence of immunocompetent cells in tissues and clinical features consistent with hypersensitivity. In the future, our understanding of titanium allergy would be advanced by a comparison of histologic features in symptomatic and asymptomatic patients with titanium implants in the maxillofacial region. Sensitivity to titanium is characterized by the local presence of abundant macrophages and T lymphocytes and the absence of B lymphocytes, indicating Type 4 hypersensitivity. The amount of titanium ion released from titanium alloys has been considered small because of the surface stabilization and the corrosion resistivity of titanium oxide formed on the surface of titanium alloys. These results may explain the rare case of contact sensitization to titanium. Incidence of titanium sensitivity is increasing as its use in dentistry is increasing day by day. Hence research is now focused on designing alternative substitutes to titanium.

7. Conclusion

Titanium is used in many fields including dentistry mainly as dental implants. With the increase in the use of titanium, there has been biological concerns as well. Thus leading to an increase in the studies evaluating titanium toxicity in the recent years, necessitating the focus on titanium safety and toxicity in the field of dentistry. Titanium dental implants can undergo corrosion and wear. Particles and ions of titanium and titanium alloy components can be deposited in surrounding tissues, and inflammation reactions can occur due to corrosion and wear. Various clinical studies have reported allergic reactions in patients who have received titanium implants and the improvement, disappearance of symptoms following the removal of titanium implants. Therefore it can be concluded that use of titanium as a dental implant material should be considered with caution, particularly in patients who are prone to metal allergy.

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