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Allergic Contact Dermatitis Induced By Titanium Dental Implants: A Review

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Abstract: *Although titanium is known for its exceptional and numerous advantageous properties, a lot of recent investigations and studies have revealed illustrations of metal sensitivity brought about by Titanium containing materials and hence proves a relation between titanium and Allergic Contact Dermatitis. Attention is needed towards the development of new and precise method for early diagnosis of titanium allergy and to find out the alternative biomaterial which can be used in place of titanium.*

Key-words: *Titanium, contact dermatitis, dental implants*

Introduction:

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I. Introduction

Allergic contact dermatitis is seen when a substance to which a person is sensitive (allergen) triggers an immune reaction in the skin[1,2]. It usually affects only the area that comes into contact with the allergen[1,2]. But it may be triggered by something that enters your body through foods, flavorings, medicine, or medical or dental procedures (systemic contact dermatitis)[2]. ACD is viewed as the most common type of immunotoxicity in people[3,4]. The instruments by which these responses happen are intricate, with numerous degrees of fine control. Their immunology focus' on the connection of immunoregulatory cytokines and discrete subpopulations of T lymphocytes. Regular allergens related with ACD are Bacitracin, Balsam of Peru, Chromium, Gold, Titanium, Nickel and so forth[5].

Titanium is often used either as the pure metal, or in an alloyed form in aerospace applications, and in medical and dental work[6-8]. It is commonly alloyed with other metals such as Vanadium (V) and Aluminum (Al). It works as a light-weight but at the same time as strong alloys for the fabrication of oral implants or the frameworks for FDPs.According to the American Society of Testing Materials (ASTM), cpTi is available in four different grades (Grade I-IV) that is based on the incorporation of small amounts of oxygen, nitrogen, hydrogen, iron and carbon during purification procedures, where each grade has different physical and mechanical properties. Grades I and II are the most commonly used cpTi types for the production of metal-ceramic FDPs. In oral implants and implant-supported FDPs, cpTi and its alloys exhibit remarkable advantages due to their excellent biocompatibility, corrosion resistance, high strength, and low modulus of elasticity[6,7,9,10].

Relation between Contact Dermatitis and Titanium

Titanium has high protection from consumption in a physiological situation and has a magnificent biocompatibility that gives it a detached, stable oxide film; because of this reason, it is considered as the material of choice for intraosseous use in restorative field. Aside from its property there are evidences which show titanium as an allergen[11]. An unfavorably susceptible response, or hypersensitization, is characterized as an unreasonable insusceptible response that happens when it encounters a known antigen. Titanium to incite an unfavorably susceptible response, must have antigenic properties and must be in contact with the creature[12-15]. The inclusion of titanium inserts and their invariability in the human body improves the measure of interior presentation and it has been demonstrated that titanium particles pack in tissues encompassing dental and orthopedic inserts, just as in local lymph nodes and respiratory tissue[11,14-16]. Recent investigations have revealed instances of unfavorably susceptible side effects such as Contact Dermatitis brought about by titanium-based

materials[11,14-16]. The measure of titanium in items has expanded with advances in purifying innovation, subsequently giving more chances to people to be sharpened to this metal. Thomas et al.[17]revealed a patient who created skin inflammation upon titanium-based osteosynthesis. Egusa et al.[18]detailed facial skin inflammation in relationship with a titanium dental embed. In their audit, Siddiqi et al.[19]proposed that titanium can cause Allergic Contact Dermatitis leading to implant failure.

Allergic Reactions to Titanium:

Metals in their iconic form can be bonded with local proteins to shape haptenic antigens, or can trigger the degranulation of mastocytes and basophiles, being fit for creating type I or type IV hypersensitive reactions. Many authors have listed various allergic reactions to titanium and they are listed below in the following table:

Authors	Allergic Reactions
Hensten-Peterson(1992)[20] Lhotka et al. (1998)[21] Valentine-Thon and Schiwara(2003)[22]	Urticaria, eczema, edema, redness and pruritus of the skin or mucosa, either localized, at distant sites, or generalized .
Tamai et al. (2001)[23]	Atopic Dermatitis
Thomas et al. (2006)[24]	Impaired healing of fractures
Haugen et al. (1996)[25]	Pain, necrosis and weakening of orthopedic implants
Matthew et al., Bircher et al. (1998)[26,27]	Facialerythema
Mitchell et al. (1990)[28]	Non-keratinized, edematous, proliferative hyperplastic tissue.

Various studies done by Authors to display allergic reactions caused by titanium are listed below:

1) Ungersboeck et al[29] tested tissue response in both symptomatic and asymptomatic with titanium orthopedic bone plates used for fixation of long bone fractures. Light microscopy examinations revealed chronic granulomatous inflammatory reactions in tissues with constant complains from the patients about persistent pain at the site of fracture.
2) Lim et al[30] studied allergic contact stomatitis caused by titanium nitride-coated implant abutment and his study revealed allergic contact stomatitis due to titanium nitride-coated implant abutments.
3) Lalor et al[15] examined tissue samples removed from the joint capsule of 5 patients after hip revision surgery were examined by immunohistochemical methods. He found the following reactions to the study:

a) Hypersensitivity to titanium was reported
b) T-cells and macrophages were present within the tissues with few B-cells or plasma cells suggesting a cell mediated immune response within the tissues adjacent to the prosthetic joints.
c) Negative skin patch test results were obtained with dilute solutions of titanium salts in all 5 patients, but there were 2 positive skin patch tests with an ointment containing titanium.
d) A proliferative soft tissue reaction adjacent to commercially pure titanium endosseousimplant abutments has also been reported.

4) Pigatto et al[31] reported ina clinical case that exfoliative cheilitis caused by mercury containing dental amalgam in close proximity to dental titanium implant in a 41 year old woman and he noticed a strong temporal relation between last titanium dental implant and the onset of exfoliative cheilitis.
5) Egusa et al[18] demonstrated a clinical case in which there was an emergence of facial eczema in association with a titanium dental implant placed for a mandibular overdenture supported by 2 implants and complete remission was achieved by the removal of titanium material. His clinical case raised a possibility that in rare circumstances, for a few patients, the use of titanium dental implants may induce an allergic reaction.

The orofacial regions have been affiliated with types I, III, and IV allergies. Type IV is one of the most widely recognized allergies found in the oral cavity, which display characteristic features related to the allergy, starting from a few days to several years from contact with allergens.

Diagnostic tests for Allergy:

Before and After implant placement People having a history of allergy to metals or jewelry and numerous patients suffering from multiple allergies have a greater risk of developing a hypersensitivity reaction to a metal implant. Although, titanium allergy has a low predominance rate, for patients with a past history of hypersensitivities, it might be better to do a metal allergy assessment and allergy testing before placing a permanent implant. This preassessment is going to help doctors diagnose a case better will prevent implant failures due to an allergic reaction to titanium. Studies have shown that infection and overload are the most prevalent reasons for an implant failure. However, there are few exceptions to this widely studied causes. Failures such as spontaneous rapid exfoliation of the implant, or the successive implant failure in the same patients, known as "cluster phenomenon", are identified without any sign of infection or overload risk factor[32]. It was accorded by the authors, that there might be an unidentified systemic determinant of failure in such cases. An unfavorably susceptible allergic response can be sensibly suspected after the placement of a dental implant, based on signs or indications related with allergy, for example, rash, urticaria, pruritus, swelling in the orofacial

area, oral or facial erythema, eczematous lesions of the cheeks or hyperplastic sores of delicate tissue (the peri-embed mucosa). Allergy testing should be a priority in such cases and should be performed without fail.

Diagnostic Tests for Titanium Allergy:

Different analytic tests are observed in the literature. It is hard to analyze the outcomes from various investigations identified with titanium allergies, since some allude to the utilization of patch tests, while others use prick tests as well as blood tests. Few regularly practiced tests by people are described below:

Patch test:

Very few positive responses to titanium havebeen shown with skin Patch tests.

75% affectability with patch test is seen for type IV metal allergy. It has been suggested by a few authors that 0.1% and 0.2% titanium sulfate solution and 0.1% and 0.2% titanium chloride are successful reagents for the skin-patch tests makeup a valuable alternative to the titanium oxide normally used for patch testing, however so far, no definite study related to dental implants allergies has been reported yet.

Memory lymphocyte immuno-stimulation assay test

The MELISA test has been validated to detect sensitization to titanium and other metals, but lack of specificity in seen in lymphocyte proliferation. MELISA is the most commonly accepted test to detect sensitization to titanium and various other metals, but a lack of specificity in lymphocyte proliferation has been observedas a drawback. It would be profitable to have a sensitive and specific test that could help in the diagnosis of titanium sensitization or allergy.

Blood test

Blood tests are commonly used in the diagnosis of a type IV allergy

Lymphocyte transformation test

Invitro testing with the Lymphocyte transformation test (LTT) measure lymphocyte proliferation following contact with an allergen and it depends on the tritiated thymidineincorporation by lymphocytes. It has also been noticed that some non-relevant proliferation of lymphocytes might happen in non-sensitized patients, leading to some false-positive results

II. Discussion

Examinations have been done about hypersensitivity responses with titanium orthopedic inserts; thus, it isn't sure regarding what degree the disclosures can be extrapolated to the oral cavity and dental implants. The intraosseous contact surface is smaller in dental inserts when compared with orthopedic ones, which might be especially significant thinking about that bone has a low reactivity potential[33-35]. Then again, oral mucosa and the skin carry on in all respects uniquely in contrast to an immunological perspective, somewhat as a result of the impact of explicit immune systems for every organ, for example, skin-related lymphoid tissue and mucosa-related lymphoid tissue. A functional application is that, the quantity of Langerhans' cells, in mucosa which go about as antigen-exhibiting cells, is a lot smaller. It is a result of this, and maybe additionally as a result of its decreased penetrability, that oral mucosa must be presented to allergen focuses 5-12 times more prominent than the skin so as to cause tissue microscopic responses. In addition, contact between the metal and the host is hampered, as the implant and prosthetic structures in the oral cavity are covered with a layer of salivary glycoprotein, which behave as a defensive barrier.

It is extremely vital to comprehend the contrast between the presence of immunocompetent cells in tissues and clinical featuresconstant with hypersensitivity. We will have a better understanding of titanium allergy in the coming years by comparing histologic features in symptomatic and asymptomatic patients with titanium implants in the maxillofacial region[33-35]. The local presence of excessive macrophages and T lymphocytes and the absence of B lymphocytes, indicating Type 4 hypersensitivity are all indicators of titanium sensitivity. Investigations are happening to develop a technique with the aid of flow cytometry, for detecting the activation of lymphocytes stimulated by a metal, and measuring different mediators like cytokines, inflammatory mediators released in response to metals.

Ikarashi et al.,[36]through his assessments on skin sensitization caused by nickel, chromium, titanium and zirconium salts demonstrated that a fundamentally enormous measure of titanium ion was required to cause a skin response. The surface stabilization and the corrosion resistivity of titanium oxide formed on the surface of titanium alloys has led to the conclusion that the amount of titanium ion released from these alloys is relatively small in measure. These findings may help us identify the causes behind the rare case of contact sensitization to titaniumTitanium sensitivity has increased significantly in the past few years due to its elaborate utilization in dentistry. Researches have now been subjected specifically in assembling elective substitutes to titanium. The

most popular novel materials, Polytheretherketone (PEEK)[37] is partially crystalline polyaromatic linear thermoplastic (ordinarily of 30-35% crystallinity) in nature. A superior set of qualities for biomaterials is offered by PEEK which includes magnificent mechanical properties.It has been revealed by various studies performed on this that implantable grade PEEK has bone framing limit which ispractically identical to rough titanium[38].

Future prospects in the diagnosis of sensitization or allergy to titanium

Interleukin-17 (IL-17) and Interleukin-22 (IL-22) are delivered by a subset of an as of late characterized T-cell line, known as Th-17. IL-17 has been related with numerous inflammatory conditions in people, including rheumatoid joint pain, organ dismissal and asthma. It has been demonstrated that the quantity of Th-17 cells and the outflow of IL-17 were fundamentally increased in positive patch test biopsies, irrespective of the nature of the antigen. IL-22 is a basic mediator in mucosal host defense and has complex anti-inflammatory, pro-inflammatory and autoimmune system impacts. It has been demonstrated that patients with contact dermatitis to nickel had a fundamentally higher IL-22 blood level, contrasted and control, showing a conceivable contribution of IL-22 in the pathogenesis of human allergic susceptible contact dermatitis. It is fascinating to build up a blood test, in view of the estimation of the creation of IL-17 as well as IL-22 by lymphocytes, so as to have the option to determine and diagnose with certainty a sensitization to titanium.

III. Conclusion

The tremendous advancements and growth in the healthcare industry, with increased life expectancy of the population expects and demands that the design of implant biomaterials demonstrates none or negligible detrimental effects on the host tissues. In spite of the fact that titanium and its alloys are considered as the oldest and traditional materials which are characterized by their wide usage and osseointegration, there are few concerns raised such as such as metal ion and debris release; allergic responses and sensitization. It is advisable to have an even more detailed research and improved knowledge for jotting down the exact causes of allergy and development of new diagnostic tools for allergic reaction of Titanium. It is extremely important to find a substitute to titanium to be able to be sure that no patient suffers from any kind of infections or allergies with it, and PEEK is one such alternative to titanium which could provide a versatile foundation material that could be later suited for a particular purpose through readily tailoring its bulk or surface properties.

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