

Titanium Hypersensitivity

A Hidden Threat for Dental Implant Patients?

Hakan Bilhan, Ph.D., D.D.S.; Canan Bural, Ph.D., D.D.S.; Onur Geckili, Ph.D., D.D.S.

ABSTRACT

Titanium and its alloys have been widely used for dental prosthetic devices because of their superior mechanical properties and biocompatibility. However, the incidence of titanium hypersensitivity or allergy is still unknown and the discussion about its existence is ongoing. Unexplained implant failures have also forced dental clinicians to investigate the possibility of titanium hypersensitivity or allergy. This review focuses on the potential of dental implant-related titanium hypersensitivity or allergic reactions. It includes an examination of the existing scientific literature and current knowledge. Evidence-based data and studies related to titanium hypersensitivity in dental implant patients are also discussed.

Titanium (Ti) and Ti alloys have been widely used in several fields of clinical medicine and dentistry during the last three decades. There are also Ti-Aluminum (Al)-vanadium (V) alloys (Ti-Al-V), Ti-Cobalt (TiCo) and other alloys under an assortment of trade names on the market today. Also “pure Ti” may be used in implant materials and spectacle frames.¹ Ti and Ti alloys have an intraosseous use in the medical field.²⁻⁵ In dentistry, Ti and Ti alloy

dental implants have been used with success as root forms that are left under mucosa for several months before they are used to support a prosthesis. Ti alloys also have a wide range of uses in cast denture frameworks or orthodontic brackets.⁶

Ti is a highly reactive metal and a thin, stable protective oxide film layer is formed spontaneously on its surface. It has been claimed that this oxide layer provides a high corrosion resistance and excellent biocompatibility.^{6,7} In a recent in vitro corrosion study, it was shown that a pure Ti surface is instantly passivated in contact with salivary proteins and exhibits a highly stable behavior.⁸ Because of these favorable properties, it has been previously stated that as a biologically and chemically inert material, Ti does not cause reactions in the body, with specific emphasis on allergic reactions.^{6,9-11} The low dissolution rate and near chemical inertness of Ti dissolution products allow bone to thrive and, therefore, osseointegrate with Ti.⁶ Therefore, Ti is generally considered the material of choice for both dental and orthopedic implantation.

Contrary to the belief that Ti and Ti alloys are non-allergenic, many questions have been raised about its biocompatibility. Ti hypersensitivity has been described in deodorant and cosmetics users,^{9,12} after local reactions to pacemakers,^{11,13-18} in patients with bronchopulmonary pathology through exposure to Ti powder,¹⁹⁻²³ in monitored hip prosthesis patients,²⁴ in failed hip and knee prostheses^{25,26} and in patients with Ti plate osteosynthesis.^{27,28} Although Ti and Ti alloy implants have corrosion

rates that are markedly less than other metallic implants, they do release Ti into the body.⁶ Degradation products of metallic biomaterials, including Ti, may mediate metal hypersensitivity or allergic reactions in the body. Many clinical reports of incompatibility reactions regarding contact dermatitis or granulomatous reactions to Ti materials, including dental implants, have been published.^{9,13,17-20,26,27,30-33} Discussion about the existence of Ti allergy is ongoing.

This article describes the potential mechanism of possible hypersensitivity reactions caused by dental implant-related Ti and Ti alloys in the human body and examines current scientific knowledge about Ti hypersensitivity.

Mechanism of Hypersensitization

An allergic reaction, or hypersensitization, is defined as an excessive immune reaction that occurs when coming into contact with a known antigen.³⁴

A hypersensitivity reaction to a metal depends upon the presence of released ions following ingestion, skin or mucosal contact, or from implant corrosion processes.^{35,36} Identification of the exact process responsible for released metal ion levels and their clinical effects are difficult to assess, depending on such factors as the material, the environment or clinical symptoms.³⁶⁻³⁹

Metal ions are released from prostheses by numerous mechanisms, including corrosion, wear and mechanically assisted electrochemical processes, such as fretting corrosion, stress corrosion and corrosion fatigue. Released ions or the implant metal degradation products bind with native proteins,³⁶ acting as haptenic antigens (allergens) and cause hypersensitivity reactions by activating the immune system.^{36,40}

Placing permanent metal dental implants might provoke such hypersensitivity reactions. Hypersensitivity might be either an immediate (within minutes) humoral response (initiated by an antibody or antibody-antigen complexes of Type I, II and III reactions) or a delayed (within hours to days) T cell-mediated response (Type IV reaction) after exposure to the immunogen.¹⁰ Implant-related metal hypersensitivity reactions are reported to be generally of Type IV delayed hypersensitivity.^{36,40} In cases indicating hypersensitivity reactions susceptible to Ti implants, delayed Type IV hypersensitivity reactions have previously been reported.^{28,31,41} Type IV hypersensitivity reactions, with Ti particles inside the macrophage lysosomes have been shown in previous reports.^{3,27,29,30,42-44}

In cases of Ti hypersensitivity or allergy, the medical literature has described cases showing symptoms of urticaria, eczema, edema, redness and pruritus of the skin or mucosa, either local-

ized, at distant sites or generalized.^{10,12,16,28,45-48} In special cases, allergic reactions have been associated with more serious problems, such as atopic dermatitis,¹² impaired healing of fractures,²⁸ pain, necrosis and weakening of orthopedic implants⁴⁵ and tolerance phenomena.⁴⁷ Facial erythema^{19,27,43} and non-keratinized, edematous, proliferative hyperplastic tissue³⁰ have been also reported in dental implant patients.

Animal studies have also shown that after placing dental implants, an increased presence of Ti ions both in peri-implant tissues^{49,50} and in the regional lymph nodes and in the lungs have been found.^{3,49,51,52} In one of the studies where two implants had failed without any infection, the related patients revealed a 2.2- to 3.8-times higher presence of Ti in the lungs, and 7- to 9.4-times higher in the lymph nodes, which were enlarged.³

Due to its poor solubility,^{29,53} a significant rise of Ti levels in blood was not detected when three dental implants were placed in humans.⁴ On the other hand, a significant rise of Ti levels in blood has been shown in patients with failed, loose Ti hip prosthesis, compared with controls.³⁹

In mucosa, the number of Langerhans' cells, which act as antigen-presenting cells, is much smaller;^{40,47,54} thus, oral mucosa must be exposed to allergen concentrations 5- to 12-times greater than the skin in order to cause tissue reactions. Concentrations of between 100 ppm and 300 ppm have been discovered in peri-implant tissues, often accompanied by discolorations, which can be well tolerated.^{13,27,36,55-57} Moreover, contact between the metal and the host is not continuous, as the implant and prosthetic structures in the oral cavity are coated with a layer of salivary glycoproteins, which act as a protective barrier.^{8,54}

Diagnosis of Ti Allergy

The diagnosis of metal allergy is typically based on the patient's medical record, clinical findings and results from epicutaneous patch tests.^{54,58} It has been suggested that the susceptibility to metal is probably genetic.⁴⁷

Metal sensitivity is conventionally diagnosed using a patch-test where an allergen is applied to the skin for a few days. A positive response is considered when an erythematous reaction is observed. However, this test is unreliable, as it may give false-positive or false-negative results because of the exceptional protective and sealing qualities of the skin against direct contact.⁵⁹ From an immunological point of view, oral mucosa and the skin behave very differently due to the influence of specific immune systems for each, such as skin-associated lymphoid tissue and mucosa-associated lymphoid tissue. A practical application is that the number of Langerhans' cells, acting as antigen-presenting cells, is much smaller in mucosa.^{40,47,54}

Epicutaneous tests, which are considered standard procedures,⁴⁷ are widely used to assess Type IV hypersensitivity reactions to Ti.^{18,19,28,29,32,34,35,40,46,58} These tests are acceptable as

proof of sensitivity to a specific allergen⁵⁴ and can also be used in combination with the intra-dermal inoculation of the antigen¹⁸ to assess Type I hypersensitivity reaction.

Blood tests have also been used, the most common being the lymphocyte transformation test (LTT),^{18,25,28,36,37,48,57,60} the memory lymphocyte immunostimulation assay (MELISA)⁴⁸ and the lymphocyte migration inhibition test (LMI or LIF).^{24,25,36}

Dentists should consider that most of their patients can suffer from multiple allergies and individuals with previous reactions to metals or jewelry have a greater risk of developing a hypersensitivity reaction to a metal implant.³⁶

Discussion

The discussion about the existence of Ti allergy or hypersensitivity is a popular one in dental implantology, because there are few clinical reports of dental implant failures arising from susceptibility to Ti.^{19,27,30,41,43,61} These reports were only suggestions, not confirmed by skin or blood tests. A recent clinical study⁶² reported a positive hypersensitivity reaction to Ti in 9 patients out of 1,500 with a prevalence of 0.6% in the post-implant insertion period, by the use of epicutaneous tests.

Scientific evidence of the clinical features of metal allergy should be based on cohort studies, case series and isolated clinical cases. It is estimated that cutaneous hypersensitivity to metals ranges between 10% and 15%.^{36,37} Studies that have used epicutaneous tests have indicated that the percentage of individuals with Ti hypersensitivity was 1% to 3%.^{34,46} Another study that used LMI blood test reported a finding of 4%,²⁴ while those performed with the MELISA test fluctuated between 1.5% and 28%, indicating that an increase in sensitization was observed in the majority of the recent studies.⁴⁸ An in vitro study reported no significant differences between MELISA and conventional LTT in terms of sensitivity and specificity and suggested that these tests are not useful in the diagnosis of metal-related contact allergy because of the high number of false-positive results.⁶³ However, in this study, no direct comparison in a single patient was given to directly compare these two tests. The only thing shown was the mean for the whole group, which we think is not a precise way to present such data. Direct comparison between MELISA and LTT has been described in a more recent study,⁴⁸ which showed data on the effect of the lymphocyte concentration in LTT tests. MELISA uses one million cells per well, while conventional LTT uses 200,000 cells per well. Thus, the sensitivity in MELISA was found to be much higher. Although MELISA is the only standardized and widely published LTT test, it is not yet approved as routine for testing Ti hypersensitivity.⁶³

Many of the investigations on the Ti hypersensitivity topic have been carried out with Ti orthopedic implants; therefore, it is not certain to what extent the findings should be extrapolated to the oral cavity and dental implants. Since reports of

Ti hypersensitivity or related pathology after dental implant insertion are scarce, the percentage for the possibility of a dental implant-related hypersensitivity reaction is suspected to be low.²⁹ Although there are various case reports with symptoms reminiscent of Ti hypersensitivity after insertion of orthopedic metal implants, the number of reported cases for dental implant patients is limited. This situation might depend upon the differences between dental or orthopedic implants. The intraosseous contact surface is much smaller in dental implants than in orthopedic implants,^{2,64} which may be particularly important when considering that bone has a very low reactivity potential.⁴⁰ Besides, the mechanisms that lead to degradation or release of Ti ions from orthopedic implants, such as wear or fretting corrosion, is not valid for dental implants.

The failure of dental implants has been widely studied,⁶⁵⁻⁶⁷ as has their use in compromised patients,^{68,69} with the primary causes being infection, impaired healing and overloading.⁶⁷ However, not all failures can be explained by these three factors; some are more difficult to explain, such as implant spontaneous rapid exfoliation⁷⁰ and other situations in which the effect of a possible hypersensitivity reaction to Ti should be taken into consideration. It was reported that unexplained pain, troublesome skin rashes,

eczema or dermatitis, impaired wound healing and sterile osteomyelitis can be observed^{28,36} and that Ti hypersensitivity could be responsible for unexplained successive failure cases of dental implants in some patients (named “cluster patients”).⁷¹ Considering the large numbers of dental implants inserted each year in the world, the extremely low number of clinical reports seems to suggest a negligible threat. As a routine practice, a failed dental implant is substituted with a new one either immediately or after a certain waiting period. Although there are numerous clinical studies reporting implant failures, probable causes of failures and percentages of implant success, there are no studies reporting symptoms of a hypersensitivity reaction after the replacement of a dental implant. On the other hand, there are no reported cases where all inserted implants somehow failed. In a case having true Ti hypersensitivity, it can be expected that all inserted dental implants would fail.

Considering the clinical experience in our university clinic, reevaluating the roughly 1,500 implants placed in the last decade, no exact hypersensitivity case has been identified. All failed implants have been replaced by new implants; they have shown a noteworthy 100% success rate. In a hypersensitivity condition, those and also other implants in the same patient would have

failed a second time. However, the probability that Ti can elicit a hypersensitivity reaction in patients still cannot be neglected. It is advisable that clinicians carry out allergy tests for such patients before placing Ti and Ti alloyed dental implants. It should be pointed out that there is a need for long-term clinical and radiographic follow-up of all dental implant patients with a history of metal allergy.

There are no epidemiological studies on the prevalence rate of Ti hypersensitivity in the general population, although the fact that external exposure to Ti is so important. Immune sensitivity may manifest at some distance from the implant, and may even demonstrate a systemic reaction that remains unnoticed or may be incorrectly interpreted.^{24,72} A hypersensitization reaction may take months or even years to develop⁴⁵ and, along with the infrequency and uncertainty of the symptomatic expression, it might be hard to recognize.^{36,37} This situation creates difficulty in performing studies about Ti allergy. Unless there are reports or case series indicating such hypersensitivity reactions, the topic will remain controversial. Further clinical studies are suggested for this purpose.

Conclusion

Since evidence-based data or studies related to Ti hypersensitivity in dental implant patients is lacking, Ti as a dental implant material cannot currently be considered a clinical threat. However, the probability that Ti or Ti alloy dental implants can elicit a hypersensitivity reaction should always be kept in mind. When unexplained successive failures of dental implants are encountered, the patient should also be medically consulted for a hypersensitivity reaction to Ti. *✍*

Queries about this article can be sent to Dr. Geckili at geckili@istanbul.edu.tr.

REFERENCES

1. Forte G, Petrucci F, Bocca B. Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention. *Inflamm Allergy Drug Targets* 2008;7:145-162.
2. Akagawa Y, Abe Y. Titanium: the ultimate solution or an evolutionary step? *Int J Prosthodont* 2003;16:28-29.
3. Frisken KW, Dandie GW, Lugowski S, Jordan G. A study of titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep. *Aust Dent J* 2002;47:214-217.
4. Smith DC, Lugowski S, McHugh A, Deporter D, Watson PA, Chipman M. Systemic metal ion levels in dental implant patients. *Int J Oral Maxillofac Implants* 1997;12:828-834.
5. Sykaras N, Iacopino AM, Marker VA, Triplett RG, Woody RD. Implant materials, designs, and surface topographies: their effect on osseointegration. A literature review. *Int J Oral Maxillofac Implants* 2000;15:675-690.
6. Powers JM, Sakaguchi RL. Dental Implants. In Powers JM, Sakaguchi RL eds. *Craig's Restorative Dental Materials*. 12th ed. pp 555-569. Philadelphia: C.V. Mosby Co. 2006
7. Sarmiento-González A, Encinar JR, Marchante-Gayón JM, Sanz-Medel A. Titanium levels in the organs and blood of rats with a titanium implant, in the absence of wear, as determined by double-focusing ICP-MS. *Anal Bioanal Chem* 2009;393:335-343.
8. Bilhan H, Bilgin T, Kadir AF, Yuksel B, Von Fraunhofer JA. The effect of mucine, IgA, urea, and lysozyme on the corrosion behavior of various non-precious dental alloys and pure titanium in artificial saliva. *J Biomater Appl* 2007;22:197-221.
9. Basketter DA, Whittle E, Monk B. Possible allergy to complex titanium salt. *Contact Dermatitis* 2000; 42:310-311.

10. Hensten-Petersen A. Casting alloys: side effects. *Adv Dent Res* 1992;6:38-43.
11. Syburra T, Schurr U, Rahn M, Graves K, Genoni M. Gold-coated pacemaker implantation after allergic reactions to pacemaker compounds. *Europace* 2010;12:749-750.
12. Tamai K, Mitsumori M, Fujishiro S, et al. A case of allergic reaction to surgical metal clips inserted for postoperative boost irradiation in a patient undergoing breast conserving therapy. *Breast Cancer* 2001;8:90-92.
13. Abdallah HI, Balsara RK, O'Riordan AC. Pacemaker contact sensitivity: clinical recognition and management. *Ann Thorac Surg* 1994;57:1017-1018.
14. Akaki T, Dekio S. Pacemaker dermatitis: report of a case. *Environ Dermatol* 2002;9:153-157.
15. Buchet S, Blanc D, Humbert P, et al. Pacemaker dermatitis. *Contact Dermatitis* 1992; 26: 46-47.
16. Peters MS, Schroeter AL, van Hale HM, Broadbent JC. Pacemaker contact sensitivity. *Contact Dermatitis* 1984;11:214-218.
17. Verbov J. Pacemaker contact sensitivity. *Contact Dermatitis* 1985;12:173.
18. Yamauchi R, Morita A, Tsuji T. Pacemaker dermatitis from titanium. *Contact Dermatitis* 2000; 42:52-53.
19. Bircher AJ, Stern WB. Allergic contact dermatitis from "titanium" spectacle frames. *Contact Dermatitis* 45: 2001; 244-245.
20. Breton JL, Louis JM, Garnier G. Asthma caused by hard metals: responsibility of titanium. *Presse Med* 1992;21:997.
21. Nemery B. Metal toxicity and the respiratory tract. *Eur Respir J* 1990;3:202-219.
22. Redline S, Barna BP, Tomashefski JF Jr, Abraham JL. Granulomatous disease associated with pulmonary deposition of titanium. *Br J Ind Med* 1986;43:652-656.
23. Shirakawa T, Kusaka Y, Fujimura N et al. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. *Chest* 1989;95:29-37.
24. Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. *Clin Orthop Relat Res* 1996;326:71-79.
25. Cook SD, McCluskey LC, Martin PC, Haddad RJ Jr. Inflammatory response in retrieved noncemented porous-coated implants. *Clin Orthop Relat Res* 1991;264:209-222.
26. Lalor PA, Gray AB, Wright S, Railton GT, Freeman MA, Revell PA. Contact sensitivity to titanium in a hip prosthesis? *Contact Dermatitis* 1990;23: 193-194.
27. Matthew I, Frame JW. Ultrastructural analysis of metal particles released from stainless steel and titanium miniplate components in an animal model. *J Oral Maxillofac Surg* 1998;56:45-50.
28. Thomas P, Bandl WD, Maier S, Summer B, Przybilla B. Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: case report and review of the literature. *Contact Dermatitis* 2006;55:199-202.
29. Lalor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MA. Sensitivity to titanium. A cause of implant failure? *J Bone Joint Surg Br* 1991;73:25-28.
30. Mitchell DL, Synnott SA, VanDecreek JA. Tissue reaction involving an intraoral skin graft and CP titanium abutments: a clinical report. *Int J Oral Maxillofac Implants* 1990; 5:79-84.
31. Müller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence. *Neuro Endocrinol Lett* 2006;27:31-35.
32. Suhonen R, Kanerva L. Allergic contact dermatitis caused by palladium on titanium spectacle frames. *Contact Dermatitis* 2001;44:257-258.
33. Viraben R, Boulinguez S, Alba C. Granulomatous dermatitis after implantation of a titanium-containing pacemaker. *Contact Dermatitis* 1995;33:437.
34. Okamura T, Morimoto M, Fukushima D, Yamane G. A Skin Patch Test for the Diagnosis of Titanium Allergy. *J Dent Res* 1999;78:1135.
35. Ahnleide I, Björkner B, Bruze M, Möller H. Exposure to metallic gold in patients with contact allergy to gold sodium thiosulfate. *Contact Dermatitis* 2000;43:344-350.
36. Hallab NJ, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001;83:428-436.
37. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. *J Biomed Mater Res* 2001; 56:427-436.
38. Iavicoli I, Falcone G, Alessandrelli M et al. The release of metals from metal-on-metal surface arthroplasty of the hip. *J Trace Elem Med Biol* 2006;20:25-31.
39. Jacobs JJ, Skipor AK, Patterson LM et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. *J Bone Joint Surg Am* 1998;80:1447-1458.
40. Schramm M and Pitto RP. Clinical relevance of allergological tests in total hip joint replacement. In Willmann G, Zweymüller K, eds. *Bioceramics in Hip Joint Replacement*. New York: Thieme, 2000. pp 101-106
41. Egusa H, Ko N, Shimazu T, Yatani H. Suspected association of an allergic reaction with titanium dental implants: a clinical report. *J Prosthet Dent* 2008;100:344-347.
42. Katou F, Andoh N, Motegi K, Nagura H. Immuno-inflammatory responses in the tissue adjacent to titanium miniplates used in the treatment of mandibular fractures. *J Craniomaxillofac Surg* 1996;24:155-162.
43. Matthew I, Frame JW. Allergic responses to titanium. *J Oral Maxillofac Surg* 1998;56: 1466-1467.

44. Revell PA, Lalor PA. Massive exposition to titanium, but without sensitization. *Acta Orthop Scand* 1995;66:484.
45. Haug RH. Retention of asymptomatic bone plates used for orthognathic surgery and facial fractures. *J Oral Maxillofac Surg* 1996;54:611-617.
46. Lhotka CG, Szekeres T, Fritzer-Szekeres M et al. Are allergic reactions to skin clips associated with delayed wound healing? *Am J Surg* 1998; 176:320-323.
47. Thomas P. Allergological aspects of implant biocompatibility. In Willmann G, Zweymüller K, eds. *Bioceramics in Hip Joint Replacement*. New York: Thieme, 2000. pp 117-121.
48. Valentine-Thon E, Schiwara HW. Validity of MELISA for metal sensitivity testing. *Neuro Endocrinol Lett* 2003; 24:57-64.
49. Brune D. Metal release from dental biomaterials. *Biomaterials* 1986;7:163-175.
50. Wennerberg A, Ide-Ektessabi A, Hatkamata S et al. Titanium release from implants prepared with different surface roughness. *Clin Oral Implants Res* 2004;15:505-512.
51. Schliephake H, Reiss G, Urban R, Neukam FW, Guckel S. Metal release from titanium fixtures during placement in the mandible: an experimental study. *Int J Oral Maxillofac Implants* 1993;8:502-511.
52. Weingart D, Steinemann S, Schilli W et al. Titanium deposition in regional lymph nodes after insertion of titanium screw implants in maxillofacial region. *Int J Oral Maxillofac Surg* 1994;23:450-452.
53. Bianco PD, Ducheyne P, Cuckler JM. Local accumulation of titanium released from a titanium implant in the absence of wear. *J Biomed Mater Res* 1996;31:227-234.
54. Bass JK, Fine H, Cisneros GJ. Nickel hypersensitivity in the orthodontic patient. *Am J Orthod Dentofacial Orthop* 1993;103:280-285.
55. Parr GR, Gardner LK, Toth RW. Titanium: the mystery metal of implant dentistry. Dental materials aspects. *J Prosthet Dent* 1985;54:410-414.
56. Torgersen S, Gilhuus-Moe OT, Gjerdet NR. Immune response to nickel and some clinical observations after stainless steel mini plate osteosynthesis. *Int J Oral Maxillofac Surg* 1993;22:246-250.
57. Torgersen S, Gjerdet NR, Erichsen ES, Bang G. Metal particles and tissue changes adjacent to miniplates. A retrieval study. *Acta Odontol Scand* 1995;53:65-71.
58. Kusy RP. Clinical response to allergies in patients. *Am J Orthod Dentofacial Orthop* 2004;125:544-547.
59. Nasser S. Orthopedic metal immune hypersensitivity. *Orthopedics* 2007;30:89-91.
60. Carando S, Cannas M, Rossi P, Portigliatti-Barbos M. The lymphocytic transformation test (L.T.T.) in the evaluation of intolerance in prosthetic implants. *Ital J Orthop Traumatol* 1985;11:475-481.
61. Preez LA, Bütow KW, Swart TJ. Implant failure due to titanium hypersensitivity/allergy? Report of a case. *SADJ* 2007; 62: 22, 24-25.
62. Sicilia A, Cuesta S, Coma G et al. A. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin Oral Implants Res* 2008;19:823-835.
63. Cederbrant K, Hultman P, Marcusson JA, Tibblin L. In vitro lymphocyte proliferation as compared to patch test using gold, palladium and nickel. *Int Arch Allergy Immunol* 1997; 112: 212-217.
64. Brunski JB, Puleo DA, Nanci A. Biomaterials and biomechanics of oral and maxillofacial implants: current status and future developments. *Int J Oral Maxillofac Implants* 2000;15: 15-46.
65. Esposito M, Hirsch J, Lekholm U, Thomsen P. Differential diagnosis and treatment strategies for biologic complications and failing oral implants: a review of the literature. *Int J Oral Maxillofac Implants* 1999;14:473-490.
66. Esposito M, Lausmaa J, Hirsch JM, Thomsen P. Surface analysis of failed oral titanium implants. *J Biomed Mater Res* 1999;48:559-568.
67. Esposito M, Thomsen P, Ericson LE, Lekholm U. Histopathologic observations on early oral implant failures. *Int J Oral Maxillofac Implants* 1999;14:798-810.
68. van Steenberghe D. The use of oral implants in compromised patients. *Periodontol* 2000 2003; 33:9-11.
69. van Steenberghe D, Quirynen M, Molly L, Jacobs R. Impact of systemic diseases and medication on osseointegration. *Periodontol* 2000 2003; 33:163-171.
70. Deas DE, Mikotowicz JJ, Mackey SA, Moritz AJ. Implant failure with spontaneous rapid exfoliation: case reports. *Implant Dent* 2002;11:235-242.
71. Evrard L, Waroquier D, Parent D. Allergies to dental metals. Titanium: a new allergen. *Rev Med Brux* 2010;31:44-49.
72. Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. *Clin Orthop Relat Res* 1996;329:233-243.