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COMMENTARY

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From manufacturers to clinicians, the release of dental implant particles can no longer be ignored

Fadi N. Barrak BDS, FDSRCS, MBBS, DipImpDent, RCSEd, FHEA, PhD[1,2] | **Siwei Li PhD**[2]

[1]School of Medicine and Dentistry, University of Central Lancashire, Preston, UK

[2]VSS Academy Training and Education Ltd., London, UK

Correspondence
Fadi N. Barrak, School of Medicine and Dentistry, University of Central Lancashire, Preston PR1 2HE, UK.
Email: FNBarrak@uclan.ac.uk

What is known

There is increasing evidence that titanium-based dental implant complications are associated with the release of metallic elements. Many clinicians remain unconcerned about such issue, and there is currently no international standards for the evaluation of biological response to implant wear particles.

What this study adds

This opinion article provides a concise summary of the current evidence and shortcomings in the field, with the aim to raise awareness among dental implant providers.

Dental implants offer a widely accepted and viable long-term treatment option for patients with missing teeth.[1,2] Since the discovery of its biocompatibility and capability of osseointegration, titanium (Ti) and its alloys have become the gold standard and most widely used in implant dentistry.[3,4] There are implants made with other materials, this opinion paper will focus on titanium-based implants. While such implants have proven to be highly reliable and have high success rates, it is not without complications. Some implants fail due to a variety of reasons including peri-implantitis, lack of osseointegration, material wear and corrosion, and hypersensitivity.[5–7]

For any implant system on the market, a series of complex and stringent standards need to be met during various stages including in vitro testing, in vivo and clinical trials, and manufacturing. Table 1 summarises the major standards dental implant companies follow.

Authors searched publicly available compliance documentations published by major dental implant companies, including BioHorizons, Dentsply Sirona, Nobel Biocare, Osstem, and Straumann. While all companies demonstrated compliance with ISO 13485 (Medical device quality management system) during the design, development, manufacture, and distribution of dental implants (and related components), information on how tests were conducted in accordance to above-mentioned ISO standards was not readily available to public. In addition, standards for biological evaluation of medical devices such as ISO 10993 permits the use of whole implant, and thus the biological implications of free Ti-based particles and metallic ions can be overlooked.

In patients that had dental implants, Ti particles, as a product of wear and/or degradation, have been detected in both intra- and extra-oral tissues. Ti particles have been found in peri-implant bone and/or soft tissues, submucosal plaque, and in distant lymph nodes in human pilot studies.[13–15] Ti particles have also been shown in both

Fadi N. Barrak and Siwei Li contributed equally to this study.

TABLE 1 General overview of major standards dental implant companies follow.

Standard	Summary description
ISO 10993[8]	Biological evaluation of medical devices — A set of standards used for evaluating the biocompatibility of medical devices. Specific tests and biological endpoints (e.g., cytotoxicity, system toxicity, degradation) will depend on each medical device and their nature of body contact.
ISO 5832[9]	Implants for surgery (Metallic materials) — A series of ISO standards specifies characteristics of, and corresponding test methods for metallic materials used in the manufacture of surgical implants, for example, Part 2: Unalloyed titanium and Part 3: Wrought titanium 6-aluminum 4-vanadium alloy. Standards from other organization may be normatively referenced, for example, ASTM F67 (Standard Specification for Unalloyed Titanium), ASTM F136 (Standard Specification for Wrought Titanium-6Aluminum-4Vanadium).
ISO 14801[10]	Dynamic loading test for endosseous dental implants — The standard specifies a method of dynamic testing of single post endosseous dental implants of the transmucosal type in combination with their premanufactured prosthetic components. It should be noted the standard is used for fatigue testing manufactured devices and not a test of fundamental properties of materials used. If the implant has metallic coatings, static tensile and shear bonding strengths between the coating and implant surface need to be test, with reference to other standards such as ASTM F1160 (Standard Test Method for Shear and Bending Fatigue Testing of Calcium Phosphate and Metallic Medical and Composite Calcium Phosphate/ Metallic Coatings) and ASTM F1142 (Standard Test Method for Tension Testing of Calcium Phosphate and Metallic Coatings).
ISO 10271[11]	Corrosion test methods for metallic materials (Dentistry) — The standard specifies test methods and procedures to determine the corrosion behavior of metallic materials used in the oral cavity.
ISO 13485[12]	Quality management system (Medical devices) — The standard specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer and applicable regulatory requirements.

Note: It should be noted that this may not include all the tests performed by each company for each dental implant system.

animal and human studies to be present in lungs, kidneys, livers, spleen, and abdominal lymph nodes, with some suggesting that particles were transported in the bloodstream by phagocytic cells and plasma proteins to these distal organs.[16–18] Authors' own ex vivo study has demonstrated that metallic nano- and micro-sized particles were released from dental implants immediately after placement.[19] They can be seen embedded in peri-implant bone tissue as well as internalized by cells such as human gingival fibroblasts and macrophages. Another study involving human biopsies has also reported localization of Ti particles in macrophages and epithelium cells.[20] It has been suggested that in cells with phagocytized Ti particles, alterations to basic cell mechanism may occur and subsequently lead to reactive lesions such as pyogenic and/or peripheral giant cell granulomas.[21,22] Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants.[23] It is characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of surrounding supporting bone in which the implant is anchored. Peri-implantitis sites had higher concentrations of Ti particles in comparison to healthy implant sites,[24–28] while authors acknowledge that there is no definitive evidence, and there is a strong association between implant particle release and peri-implantitis.

The most common feasible causes of Ti particle release are friction during implant placement procedures, implant surface corrosion, and fretting phenomena at the implant-abutment interphase.[29] The use of dental hygiene products and antiseptic agents such as fluoride and chlorhexidine have been linked with alterations to the implant surface topography and increased corrosion.[30,31] In addition, implant debridement procedures, for example, surface cleaning with mechanical and/or chemical means, used during implant maintenances and treatment of peri-implantitis, such as implantoplasty, were also reported to be the causes of particle release.[25,32] Authors' own ex vivo study has found that the amount of metallic particle and ion release during placement was dependent on both implant material and design, where grade 5 titanium alloy (Ti-6AL-4V) implants resulted in more release compared to commercial pure (grade 4) or Roxolid® (Ti-15Zr, a Ti alloy composed of ∼15% zirconium) implants.[19] In an in vitro study that investigated particle release due to frictional wear, it was also reported that wear signs were evident in all implant-abutment couplings (grade 4 or Roxolid® implants paired with Ti or Zr abutments).[33] More interestingly, it was found that larger particles were generated in Roxolid® with Ti or Zr abutment pairings in comparison to grade 4 implants. These findings emphasize the need of careful pre-manufacturing evaluations of the implant materials and designs as there is increasing evidence of potential risks of these wear particles.

As the use of Ti and its alloy increases, concerns over their safety are also increasing as the number of research and reports focusing on Ti toxicity showed a rapid upward trend in recent years.[34] Both micro- and nano-sized particles can be generated during an implant's life span.[19,32,34] There is evidence that TiO_2 nanoparticles are associated with cellular DNA damage and pro-inflammatory effects.[35,36] It has been reported that the TiO_2 nanoparticles could adsorb CXCL8 (and IFN-γ), clinically relevant pro-inflammatory chemokines, thus resulting in the disruption of neutrophil chemotaxis and local inflammatory mediator concentration and subsequently reduced inflammatory response.[36] Particle release as an inflammation catalyst mechanism is an emerging concept in dental medicine that may help explain the pathogenesis of peri-implantitis.[27,28,37,38]

Implant losses can be associated with inflammatory complications due to Ti particles.[15,39] Peri-implant diseases can be peri-implantitis or

peri-implant mucositis, which are characterized by the presence or the lack of peri-implant bone loss, respectively. The general consensus is that peri-implant mucositis is inflammatory disease involving mucosa only, whereas peri-implantitis sites extend to supporting bone.[23] Souza and colleagues demonstrated that Ti particles affected biofilm composition, increasing population of four bacterial species (*Streptococcus anginosus*, *Prevotella nigrescens*, *Capnocytophaga sputigena*, and *Actinomyces israelli*), while Ti ions resulted in a higher level of pathogens from disease-associated complex as well as a reduction of health-associated complex.[40] This suggests Ti particles and ions may encourage the growth of peri-implant pathogenic species, resulting in subsequent microbial dysbiosis and eventually peri-implantitis.

While many tests can be performed to determine parameters such as implant surface topography, composition, and their effects on adhesion, proliferation, and differentiation of various clinically relevant cell populations, suffice it to say that the current setups in accordance to ISO and regulatory bodies do not reflect the extremely complex physiological microenvironment surrounding an implant. More importantly, the effects of Ti particle and metallic ion released from implants are often overlooked by implant companies and clinicians placing the implants. This clearly indicates a need of awareness in the field of implant dentistry as well as a reliable testing protocol that yields highly reproducible and translatable results with regards to the biological response of patients after implantation.

Some manufacturers and independent organizations have already taken steps to carry out additional standardized tests in addition to those required by regulatory bodies such as the U.S. Food and Drug Administration (FDA) and European health, safety, and environmental protection standards (CE marking). CleanImplant Foundation, for example, utilizes scanning electron microscope (SEM) and energy-dispersive x-ray spectroscopy (EDS) in a clean room environment (according to Class 100 US Federal Standard 209E, Class 5 DIN EN ISO 14644-1) to assess surface homogeneity and contaminations of implants during manufacturing and packaging process.[41] While this is an important development in the field of Implant Dentistry to acknowledge the risk of adverse effects caused by "impurities" such as Ti particles as well as organic particles originated from manufacturing and/or packaging, further biological tests and a more stringent threshold should be applied. CleanImplant argued that single organic particles smaller than 50 μm in diameter were considered less damaging than numerous particles, with a maximum of 30 particles along the circumference of the implant.[41] In addition, major plaque-like organic contaminants exceeding the size of 50 μm and PTFE particles, presumably originating from Teflon molds used during implant production, were considered unacceptable.[41] There are studies reporting the density of Ti particles to be as high as 40 million per mm^3 of tissue.[27] It should be noted however, that there may be differences in the adverse effects of impurities from defective manufacturing and particle release from appropriately manufactured implants. Further studies are required.

While some clinical/human studies, for example, by Rakic and colleagues,[42] argued that there is no clear evidence of direct pathological effects of implant particles, particles were identified in all peri-implantitis samples in this study, while another reported presence of particles in 90% peri-implant soft tissue biopsies from patients diagnosed with peri-implantitis.[43] Authors believe the prevalence of the particles depicts a strong association between Ti particles and peri-implant disease. As mentioned above that both nanometer- and micrometer-sized Ti particles can be detected in peri-implant tissues.[19,26,44] The size of particles can vary depending on the implant size, design, and material.[19,33] Authors acknowledge that it is currently unclear which particle configuration (e.g. size and surface chemistry) and location of distribution results in unfavorable biological response. It is therefore important to apply a standardized set of testing methods to each variation of the same implant system. The biological effects of wear particles, especially nanometer-sized particles, remain unclear and debatable. Some have observed positive antibiofilm properties with either Ti nanoparticles alone, or in combination with other metal nanoparticles, leading to suggestions that these nanoparticles can protect against peri-implantitis pathogens.[45,46] Ti nanoparticles have been proposed as a commercially viable anti-plaque and anti-biofilm strategy in products such as tooth pastes and mouthwashes.[47] Others on the other hand, have reported adverse effects such as induction of apoptosis, genotoxicity, collagen, and lipid deformation as well as alveolar epithelial metaplasia.[39,48,49] It has been reported that nano- and micro-sized Ti particles are associated with the activation of inflammatory response and the release of pro-inflammatory cytokines such as TNF-α and IL-1β.[50,51] In addition, Ti particles have been shown to induce M1 macrophage phenotype polarization and associated bone resorption.[52] Ti nanoparticles have been reported to initiate the TLR4 (toll-like receptor 4)-dependent pathway and the subsequent overproduction of MUC5B (mucin 5B), which is involved in the inflammatory response in human airways.[53] Although the body of evidence suggests that the biological effects of implant (nano)particles is inflammatory, more specific toxological research is needed and biomarker assays should be incorporated during the evaluation process of an implant.

Another possible cause of implant failure can be attributed to allergic reactions to titanium, albeit there is limited evidence. Hypersensitivity reactions such as erythema, eczema, necrosis, and bone loss due to Ti dental implants have been reported in some studies.[7,54,55] Concerns of adverse effects of Ti and its alloys have led to the research and development of alternative implant materials. One example is zirconia and polyaryletherketone (PEEK), which have gained increasing interest as a material in dental applications mainly due to its good biocompatibility and biomechanical characteristics.[56–58] However, further investigations are required before such material can become a viable commercial and clinical alternative to Ti. This commentary focused exclusively on titanium-based metal implants, and authors do acknowledge there is also propensity for particle release and accumulation from implants made with alternative materials.[27]

FINAL REMARK

Ti-based dental implants currently have an undisputed high survival rate clinically and will continue to be successful commercially.

However, attention now must be placed on the potential adverse effects associated with Ti implants, in particular, their wear particles. A new set of standards for the evaluation of biological response to implant wear particles and metallic ions needs to be developed with the aim to increase the predictive power of preclinical assessment of materials and dental implants. These testing data should be readily available such that clinicians as well as patients are aware of the biological and mechanical implications of materials used in dental implants. Dental implant providers, be it the manufacturers or the clinicians placing the implants, need to be aware of these potential risks and the need for additional testing standards as they inevitably bear the responsibility of the products used and treatments provided to the general public.

AUTHOR CONTRIBUTIONS

FB contributed to the conception, drafting, critical revision, and approval of article. SL contributed to the drafting and critical revision of article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Fadi N. Barrak https://orcid.org/0000-0002-3906-9174
Siwei Li https://orcid.org/0000-0002-1042-0012

REFERENCES

1. Alrabiah M, Alrahlah A, Al-Hamdan RS, Al-Aali KA, Labban N, Abduljabbar T. Survival of adjacent-dental-implants in prediabetic and systemically healthy subjects at 5-years follow-up. *Clin Implant Dent Relat Res*. 2019;21(2):232-237. doi:10.1111/cid.12715
2. Francetti L, Cavalli N, Taschieri S, Corbella S. Ten years follow-up retrospective study on implant survival rates and prevalence of peri-implantitis in implant-supported full-arch rehabilitations. *Clin Oral Implants Res*. 2019;30:252-260. doi:10.1111/clr.13411
3. Abraham CM. A brief historical perspective on dental implants, their surface coatings and treatments. *Open Dent J*. 2014;8:50-55. doi:10.2174/1874210601408010050
4. Guglielmotti MB, Olmedo DG, Cabrini RL. Research on implants and osseointegration. *Periodontol 2000*. 2019;79(1):178-189. doi:10.1111/prd.12254
5. Delgado-Ruiz R, Romanos G. Potential causes of titanium particle and ion release in implant dentistry: a systematic review. *Int J Mol Sci*. 2018;19(11):3585. doi:10.3390/ijms19113585
6. Derks J, Schaller D, Hakansson J, Wennstrom JL, Tomasi C, Berglundh T. Peri-implantitis – onset and pattern of progression. *J Clin Periodontol*. 2016;43(4):383-388. doi:10.1111/jcpe.12535
7. Siddiqi A, Payne AGT, De Silva RK, Duncan WJ. Titanium allergy: could it affect dental implant integration? *Clin Oral Implants Res*. 2011;22(7):673-680. doi:10.1111/j.1600-0501.2010.02081.x
8. International Organization for Standardization. *ISO 10993 (ICS11.100.20): Biological Evaluation of Medical Devices*. ISO; 2022.
9. International Organization for Standardization. *ISO 5832 (ICS 11.040.40): Implants for Surgery, Prosthetics and Orthotics*. ISO; 2022.
10. International Organization for Standardization. *ISO 14801: Dentistry – Implants – Dynamic Loading Test for Endosseous Dental Implants*. ISO; 2016.
11. International Organization for Standardization. *ISO 10271: Dentistry – Corrosion Test Methods for Metallic Materials*. ISO; 2020.
12. International Organization for Standardization. *ISO 13485: Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes*. ISO; 2016.
13. 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(6 Pt 2):450-452. doi:10.1016/s0901-5027(05)80045-1
14. Cionca N, Meyer J, Michalet S, Varesio E, Hashim D. Quantification of titanium and zirconium elements in oral mucosa around healthy dental implants: a case-control pilot study. *Clin Oral Investig*. 2023;27(8):4715-4726. doi:10.1007/s00784-023-05099-8
15. Kheder W, Al Kawas S, Khalaf K, Samsudin AR. Impact of tribocorrosion and titanium particles release on dental implant complications – a narrative review. *Jpn Dent Sci Rev*. 2021;57:182-189. doi:10.1016/j.jdsr.2021.09.001
16. Altuna P, Lucas-Taulé E, Gargallo-Albiol J, Figueras-Álvarez O, Hernández-Alfaro F, Nart J. Clinical evidence on titanium-zirconium dental implants: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg*. 2016;45(7):842-850. doi:10.1016/j.ijom.2016.01.004
17. Olmedo DG, Tasat D, Guglielmotti MB, Cabrini RL. Titanium transport through the blood stream. An experimental study on rats. *J Mater Sci Mater Med*. 2003;14(12):1099-1103. doi:10.1023/b:jmsm.0000004007.26938.67
18. 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(1):335-343. doi:10.1007/s00216-008-2449-2
19. Barrak F, Li S, Muntane A, Bhatia M, Crossthwaite K, Jones J. Particle release from dental implants immediately after placement – an ex vivo comparison of different implant systems. *Dent Mater*. 2022;38(6):1004-1014. doi:10.1016/j.dental.2022.04.003
20. Olmedo D, Fernandez MM, Guglielmotti MB, Cabrini RL. Macrophages related to dental implant failure. *Implant Dent*. 2003;12(1):75-80. doi:10.1097/01.id.0000041425.36813.a9
21. Halperin-Sternfeld M, Sabo E, Akrish S. The pathogenesis of implant-related reactive lesions: a clinical, histologic and polarized light microscopy study. *J Periodontol*. 2016;87(5):502-510. doi:10.1902/jop.2016.150482
22. Olmedo DG, Paparella ML, Brandizzi D, Cabrini RL. Reactive lesions of peri-implant mucosa associated with titanium dental implants: a report of 2 cases. *Int J Oral Maxillofac Surg*. 2010;39(5):503-507. doi:10.1016/j.ijom.2009.11.007
23. Berglundh T, Armitage G, Araujo MG, et al. Peri-implant diseases and conditions: consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol*. 2018;89(suppl 1):S313-S318. doi:10.1002/JPER.17-0739
24. Asa'ad F, Thomsen P, Kunrath MF. The role of titanium particles and ions in the pathogenesis of peri-implantitis. *J Bone Metab*. 2022;29(3):145-154. doi:10.11005/jbm.2022.29.3.145
25. Olmedo DG, Nalli G, Verdú S, Paparella ML, Cabrini RL. Exfoliative cytology and titanium dental implants: a pilot study. *J Periodontol*. 2013;84(1):78-83. doi:10.1902/jop.2012.110757
26. Fretwurst T, Buzanich G, Nahles S, Woelber JP, Riesemeier H, Nelson K. Metal elements in tissue with dental peri-implantitis: a pilot study. *Clin Oral Implants Res*. 2016;27(9):1178-1186. doi:10.1111/clr.12718
27. Nelson K, Hesse B, Addison O, et al. Distribution and chemical speciation of exogenous micro- and nanoparticles in inflamed soft tissue

adjacent to titanium and ceramic dental implants. *Anal Chem*. 2020;92(21):14432-14443. doi:10.1021/acs.analchem.0c02416
28. Wilson TG Jr, Valderrama P, Burbano M, et al. Foreign bodies associated with peri-implantitis human biopsies. *J Periodontol*. 2015;86(1):9-15. doi:10.1902/jop.2014.140363
29. Salvi GE, Cosgarea R, Sculean A. Prevalence and mechanisms of peri-implant diseases. *J Dent Res*. 2017;96(1):31-37. doi:10.1177/0022034516667484
30. Krishnamoorthy G, Narayana A, Balkrishanan D. Chlorhexidine for the treatment of peri-Implantitis: is it a benison? *J Long-Term Eff Med Implants*. 2022;32(1):19-23. doi:10.1615/JLongTermEffMedImplants.2021039510
31. Goutam M, Kumar S, Sushma KN, Kharat N, Shankar D, Shrivastava N. Assessment of effect of fluoride on titanium dental implants. *J Pharm Bioallied Sci*. 2022;14(suppl 1):S220-S221. doi:10.4103/jpbs.jpbs_2_22
32. Barrak FN, Li S, Muntane AM, Jones JR. Particle release from implantoplasty of dental implants and impact on cells. *Int J Implant Dent*. 2020;6(1):50. doi:10.1186/s40729-020-00247-1
33. Olander J, Ruud A, Wennerberg A, Stenport VF. Wear particle release at the interface of dental implant components: effects of different material combinations. An in vitro study. *Dent Mater*. 2022;38(3):508-516. doi:10.1016/j.dental.2022.01.001
34. Kim KT, Eo MY, Nguyen TTH, Kim SM. General review of titanium toxicity. *Int J Implant Dent*. 2019;5(1):10. doi:10.1186/s40729-019-0162-x
35. Suarez-Lopez Del Amo F, Rudek I, Wagner VP, et al. Titanium activates the DNA damage response pathway in oral epithelial cells: a pilot study. *Int J Oral Maxillofac Implants*. 2017;32(6):1413-1420. doi:10.11607/jomi.6077
36. Shi H, Magaye R, Castranova V, Zhao J. Titanium dioxide nanoparticles: a review of current toxicological data. *Part Fibre Toxicol*. 2013;10:15. doi:10.1186/1743-8977-10-15
37. Albrektsson T, Dahlin C, Jemt T, Sennerby L, Turri A, Wennerberg A. Is marginal bone loss around oral implants the result of a provoked foreign body reaction? *Clin Implant Dent Relat Res*. 2014;16(2):155-165. doi:10.1111/cid.12142
38. Fretwurst T, Nelson K, Tarnow DP, Wang HL, Giannobile WV. Is metal particle release associated with peri-implant bone destruction? An emerging concept. *J Dent Res*. 2018;97(3):259-265. doi:10.1177/0022034517740560
39. Zhou Z, Shi Q, Wang J, et al. The unfavorable role of titanium particles released from dental implants. *Nanotheranostics*. 2021;5(3):321-332. doi:10.7150/ntno.56401
40. Souza JGS, Costa Oliveira BE, Bertolini M, et al. Titanium particles and ions favor dysbiosis in oral biofilms. *J Periodontal Res*. 2020;55(2):258-266. doi:10.1111/jre.12711
41. Duddeck DU, Albrektsson T, Wennerberg A, Larsson C, Beuer F. On the cleanliness of different oral implant systems: a pilot study. *J Clin Med*. 2019;8(9):1280. doi:10.3390/jcm8091280
42. Rakic M, Radunovic M, Petkovic-Curcin A, Tatic Z, Basta-Jovanovic G, Sanz M. Study on the immunopathological effect of titanium particles in peri-implantitis granulation tissue: a case-control study. *Clin Oral Implants Res*. 2022;33(6):656-666. doi:10.1111/clr.13928
43. Berryman Z, Bridger L, Hussaini HM, Rich AM, Atieh M, Tawse-Smith A. Titanium particles: an emerging risk factor for peri-implant bone loss. *Saudi Dent J*. 2020;32(6):283-292. doi:10.1016/j.sdentj.2019.09.008
44. Safioti LM, Kotsakis GA, Pozhitkov AE, Chung WO, Daubert DM. Increased levels of dissolved titanium are associated with peri-Implantitis – a cross-sectional study. *J Periodontol*. 2017;88(5):436-442. doi:10.1902/jop.2016.160524
45. Lavaee F, Faez K, Faez K, Hadi N, Modaresi F. Antimicrobial and antibiofilm activity of silver, titanium dioxide and iron nano particles. *Am J Dent*. 2016;29(6):315-320.
46. Vargas-Reus MA, Memarzadeh K, Huang J, Ren GG, Allaker RP. Antimicrobial activity of nanoparticulate metal oxides against peri-implantitis pathogens. *Int J Antimicrob Agents*. 2012;40(2):135-139. doi:10.1016/j.ijantimicag.2012.04.012
47. Khan ST, Al-Khedhairy AA, Musarrat J. ZnO and TiO_2 nanoparticles as novel antimicrobial agents for oral hygiene: a review. *J Nanopart Res*. 2015;17(6):276. doi:10.1007/s11051-015-3074-6
48. Kuku G, Culha M. Investigating the origins of toxic response in TiO_2 nanoparticle-treated cells. *Nanomaterials (Basel)*. 2017;7(4):83. doi:10.3390/nano7040083
49. Wang JJ, Sanderson BJ, Wang H. Cyto- and genotoxicity of ultrafine TiO_2 particles in cultured human lymphoblastoid cells. *Mutat Res*. 2007;628(2):99-106. doi:10.1016/j.mrgentox.2006.12.003
50. Pettersson M, Kelk P, Belibasakis GN, Bylund D, Molin Thorén M, Johansson A. Titanium ions form particles that activate and execute interleukin-1β release from lipopolysaccharide-primed macrophages. *J Periodontal Res*. 2017;52(1):21-32. doi:10.1111/jre.12364
51. Barrak FN, Li S, Mohammed AA, Myant C, Jones JR. Anti-inflammatory properties of S53P4 bioactive glass implant material. *J Dent*. 2022;127:104296. doi:10.1016/j.jdent.2022.104296
52. Wang X, Li Y, Feng Y, Cheng H, Li D. Macrophage polarization in aseptic bone resorption around dental implants induced by Ti particles in a murine model. *J Periodontal Res*. 2019;54(4):329-338. doi:10.1111/jre.12633
53. Kim GO, Choi YS, Bae CH, Song SY, Kim YD. Effect of titanium dioxide nanoparticles (TiO_2 NPs) on the expression of mucin genes in human airway epithelial cells. *Inhal Toxicol*. 2017;29(1):1-9. doi:10.1080/08958378.2016.1267282
54. Singh R, Lehl G, Hussain AB, et al. Prevalence of titanium hypersensitivity in patients with titanium implants: a systematic review and meta-analysis. *J Pharm Bioallied Sci*. 2021;13(suppl 2):S1345-s1349. doi:10.4103/jpbs.jpbs_159_21
55. Müller-Heupt LK, Schiegnitz E, Kaya S, Jacobi-Gresser E, Kämmerer PW, Al-Nawas B. Diagnostic tests for titanium hypersensitivity in implant dentistry: a systematic review of the literature. *Int J Implant Dent*. 2022;8(1):29. doi:10.1186/s40729-022-00428-0
56. Ayyadanveettil P, Thavakkara V, Latha N, Pavanan M, Saraswathy A, Kuruniyan MS. Randomized clinical trial of zirconia and polyetheretherketone implant abutments for single-tooth implant restorations: a 5-year evaluation. *J Prosthet Dent*. 2022;128(6):1275-1281. doi:10.1016/j.prosdent.2021.02.037
57. da Cruz MB, Marques JF, Peñarrieta-Juanito GM, et al. Hard and soft tissue cell behavior on polyetheretherketone, zirconia, and titanium implant materials. *Int J Oral Maxillofac Implants*. 2019;34(1):39-46. doi:10.11607/jomi.6926
58. Vertucci V, Pacifici A, Ruggiero R, et al. In vitro comparative study on the mechanical behavior of zirconia and polyetheretherketone in applied dental sciences. *Eur Rev Med Pharmacol Sci*. 2022;26(3 suppl):106-114. doi:10.26355/eurrev_202212_30800

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