



## Review Article

## Titanium toxicity-A review

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## ABSTRACT

Titanium is a commonly used inert bio-implant material within the medical and dental fields. Although the use of titanium is thought to be safe with a high success rate, in some cases, there are rare reports of problems caused by titanium. Even though various recent advancement in the implant has been implicated in this era, still titanium is gold stranded among dental implant materials. In most of these problematic reports, only individual reports are dominant and comprehensive reporting has not been performed. This comprehensive article has been prepared to review the toxicity of titanium and its alloy materials in the field of dentistry.

**Keywords:** Allergy; implant toxicity; titanium implants; titanium particles; Yellow nail syndrome

## 1 INTRODUCTION

The biocompatibility of synthetic substances (biomaterials) and its biocompatibility in organic tissues augmentation or substitute possess a major concern in medical sector. Dental implant prosthetic reconstruction in oral-maxillofacial needs special care & skill as the devices extend from oral cavity, across the protective epithelial zones, and involving the underlying bone<sup>(1)</sup>. Branemark and colleague studied the relationship of titanium with bone, and coined the term osseointegration, a "direct contact between living bone and a functionally loaded implant surface without interposed soft tissue at the light microscopic level"<sup>(2)</sup>. Titanium is a transition metal with a silver colour, known for high strength and resistance to corrosion. Even though various metallic biomaterials have been used widely, but extensively used dental implant biomaterials is titanium and its alloys. Numerous studies have been done on implant surface treatment especially titanium and alloys for the determination of its mechanism and toxic behaviour<sup>(3,4)</sup>. One of classic examples, is inflammatory reactions induce bone loss due to titanium and allergic reactions, and yellow

nail syndrome which comprises implant corrosion<sup>(5)</sup>. This article throws light on general view of the properties, toxicity and associated risk of titanium and its alloy incorporation in dental implants.

## Biomaterials of dental implants

Many biologically compatible materials can be used for the manufacturing of implants. Currently, interest is centred on metals and metal alloys, but research continues with biomaterials such as ceramics and carbons, as well as polymers and composites<sup>(5)</sup>. The definition of biocompatibility, gives material (biomaterial) response within any sort of devices (design) for a concerned clinical application<sup>(6)</sup>. In 1970s biocompatibility was defined in terms of minimal harm to the host or to the biomaterial. At present biomaterials are fabricated with surface modification, to directly influence short- and long-term tissue responses. Bioactive coatings on biomaterials have been stated to transform from human clinical trials to surface preparation. Research area of interest has been turning its sight towards synthetic material and biological

implants combination.

### The peri implant mucosa

The peri-implant mucus around an intra-osseous implant consists of a dense collagenous lamina propria covered by stratified squamous keratinizing epithelium. Implant-epithelium junction is analogous to the junctional epithelium around natural teeth, where an epithelial cell attaches to the titanium-based implant by basal lamina and hemidesmosomes. There also evidence for an adhesive junctional epithelium attachment to ceramic implants has also been presented<sup>(7,8)</sup>. Depth of normal sulcus in an intraosseous implant is 1.5 to 2 mm. Around an implant is sulcular epithelium that is continuous apically with the junctional epithelium, along with an intact epithelium and unattached collagen fibres, running parallel to implant surface. Microscopic irregularities and porosities found on plasma-sprayed titanium surfaces may favour the appearance of fibres oriented perpendicularly to the implant surface and in turn, in specific directions<sup>(9)</sup>.

### The implant-bone interface

The endosseous implants and bone relationship consists of either one of two mechanisms: osseointegration /or fibro osseous integration, former explains the bone is in intimate but not micro-structural contact with the implant, latter explains, soft tissues such as fibres and/or cells, are intervened between the two surfaces. According to Schroder, between implant and bony interfaces, absence of connective tissue or any other tissues is called osseointegration. Histologic sections of the bone-implant interface, usually of (20 to 150 micrometre) thickness and do not permit an accurate view of the interface. These thick sections have been the primary standard of viewing the interface and may have led to the premature definition of the interface as an osteointegrative one<sup>(10)</sup>. Although some ultrastructural investigations have reported mineralized matrix in direct contact with titanium without the presence of any amorphous layer others have reported the interposition of connective tissue<sup>(11)</sup>. An amorphous, cell-free layer, ranging in width from 20 to 1000 nm, and presence of lamina limitans-like line, 50 nm in thickness and a noncalcified collagen layer adjacent to the titanium surface is observed. Complete mineralization is seen only at 2000 nm from the metal<sup>(11)</sup>.

### Toxicity and it's consideration

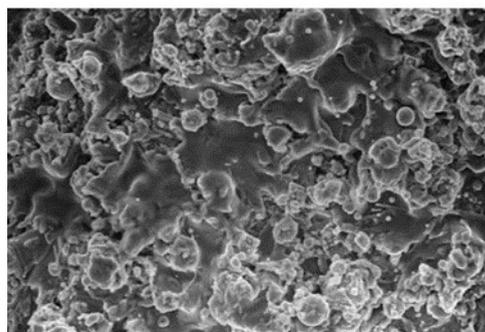
Toxicity is concerned with primary biodegradation product which involves simple and complex structure of cations & anions, particularly which are having higher atomic molecular weight. Some of factors includes in considerations are: (1) Nature of particles matter, i.e., ions and solid particles, in the tissue deposition and systemic

evidences (2) Biodegradation dissolved amount per time unit (3) Elimination of materials quantity by metabolic activity per time unit. The critical issue is that the surface represents the “finished” form of the implant<sup>(12)</sup>.

Molybdenum, cobalt, nickel are dissolved at higher concentrations, while chromium and titanium ion particles at a lower concentration. The transformation of harmful primary products is dependent on their level of solubility and transfer. Zitter and Plenk<sup>(13)</sup> stated that oxidation of anodic ions and reduction of cathodic ions in various surfaces, but through charge transfer they balance each other.

### Titanium and titanium-6 aluminum-4 vanadium

Reduction in biocorrosion also achieved in passivated condition. This will be better for implant loading in a receptor site even with a closed fitting zone. This sole property is one among consideration for incorporation of titanium in dental implants<sup>(14)</sup>. Titanium has relatively low tensile strength and modulus of elasticity when in comparison with other alloys. Certain properties like soft wrought and ductile metallurgic condition (normal plate and root form of implants) are merely 1.5 times exceptional in strength than compact bone strength. Ceramic-like coatings have been added to titanium and cobalt with titanium plasma-sprayed surfaces. A relatively new process (resorbable blast media) has been said to provide a comparable roughness to an alumina grit blast finish, which can be a rougher surface than the machined, glass-beaded, or acid-etched surfaces (Figure 1).



**Fig. 1:** Titanium plasma-sprayed surfaces result in increased total surface area, expose physical and chemical anchor system and increase load-bearing capability (scanning electron microscopy of Bio Horizons D3 implant;  $\times 500$ )

Since the tensile and elastic module property is distinguishable, this will enhance on the design of implant and proper distribution of mechanical stress. Influence of aluminum and vanadium biodegradation products on local and systemic tissue responses have been reviewed. Both the titanium and cobalt based biodegradable products are electrochemically similar; however, comparative elements in an aeration cell shows that the current flow in titanium and its alloys have magnitude lower than that in Co-

Cr alloys or Fe-Cr-Ni-Mo based materials. As specified by the ASTM F4 on surgical implants and the American Dental Association<sup>(15)</sup> critical considerations include the surface consideration, mechanical properties, and, chemical analysis.

### Interactions of titanium particles with hard and soft tissues

Oxide modification during in vivo exposure has been shown to result in increased titanium oxide layer thickness of up to 200 nm. Bone marrow site has high growth concentration, whereas titanium in contact with cortical regions of bone shows low growth concentration region. The bio-interaction properties are slow, and leads to liberation of ion particles and substrate oxide alteration. There has been reported cases of local and systemic increases of the ion concentration<sup>(16)</sup>.

### Titanium and alloys integration

Williams<sup>(17)</sup> acclaimed that titanium has excellent properties in tenacious oxide film, it is usually quite un-stable to prevent aggravating and wear in bearing systems under load. Passivating metals like titanium, vanadium, zirconium, niobium, and tantalum, resist corrosion due to the formation of a surface oxide layer. Some situations have resulted in metal-to-metal contact and local welding. Lemons et al.,<sup>(18)</sup> studied about single-stage solid implants in surface conditions, result shows that potential damage can surge corrosion resistance. Similar studies reported that, titanium alloys are evidenced to abrasion, corrosive environment and oxide changes.

### Titanium and its alloy toxicity

Presently, TiO<sub>2</sub> powder is the habitual utilized form of titanium. Various studies reported the TiO<sub>2</sub> nanoparticle toxicity present in both cultured human cell & animal models. Valentini et al.<sup>(19)</sup> study done in rat brain, reveals the toxicity of TiO<sub>2</sub>-NP on the cortical neuronal cells, and indicated the evidences of TiO<sub>2</sub>-NP toxicity in CNS.

In 1981, Rae et.al.,<sup>(20)</sup> performed experiments in which human synovial fibroblasts were exposed pure titanium and wear debris from titanium alloy (Ti-6Al-4V) including various preparations of meal and alloy. He reveals that vanadium possess more amount of soluble property in cultured cell. This shows vanadium in titanium alloy might be toxic to the cell which releases TNF, IL-1,6 and PGE<sub>2</sub> like inflammatory mediators to the surrounding prosthesis by affecting the tissues cause osteolysis. Type I or IV allergic reactions due to titanium have been a considerable factor for failure of implants in some cases (known as “cluster patients”). Between 100 and 300 ppm concentration, have been discovered in peri-implant tissues with discoloration of peri-mucosal tissues. These titanium particles could react inside with the macrophage lysosome<sup>(21,22)</sup>.

### Titanium implants toxicity

According to the American Society for Testing and Materials (ASTM), commercially pure titanium characteristically defines contrasting grades in purity, and also conflicting quantities of carbon, oxygen, nitrogen, hydrogen, and iron like interstitial elements. This CpTi acquires grade I-IV, whereas, grade V refers to the titanium alloys Ti-6Al-4V. This particle gets released from titanium implant or implant surfaces constantly to oral environment. To compensate this defect, Martini et al. compared two contrast implant materials like titanium powder plasma-spray-coated titanium screws (TPS-Ti) and fluoro-hydroxyapatite-coated titanium screws (FHA-Ti) and reported there is evidence containing liberation of titanium particles in an intra-medullary space among patients. This is more commonly seen among materials like titanium powder plasma-spray-coated titanium screws (TPS-Ti). This occurs as a result of occurrence of friction in bone-implant interface, leading to release of the detachment metal particles to surrounding tissue and integration loss<sup>(23)</sup>. Titanium particles in peri-implant soft tissues reveals a strong evidence that it induces corrosion and causes systemic toxicity. But the factor involving various environment on dental implants needed further studies. Nahles & Woelber JP et al.<sup>(24)</sup> reported that lymphocyte and M1 type macrophages detection along with increasing titanium concentration and metal particles in peri-implant soft tissue.

### Diseases related to titanium

According to a study by Berglund and Carlmark<sup>(25)</sup> in 2011, titanium can be attributed to the cause of “yellow nail syndrome” (Figure 2) which is termed by Samman and White characterised as slow, thicker, and yellowish growing of nails in conjunction with lymphedema syndrome also with recurrent pleural effusion, intermittent coughing with bronchial asthma, sputum, bronchiectasis, and inflammation in the maxillary sinus.

A general term called iontophoresis where through electrical conduction ions in a different form can be passed into body from outer surface. One of major problems for titanium ions is corrosion due to oxidation of fluorine<sup>(26)</sup> & corrosion of galvanic effects between titanium implants and other materials like gold and/or amalgam restorations. Medication such as diclofenac celecoxib, and zopiclone contains TiO<sub>2</sub>, along with gum, candy, and liquorice, after prescription of these types of drugs also some patients reported with “yellow nail syndrome”. According to Dos Santos et al.<sup>(27)</sup> in a study reported titanium accumulation in the liver, spleen, lung, lymph nodes, and bone marrow in the autopsy results of five drug-addicted patients; titanium pigmentation was observed under a microscope. This report revealed a systemic accumulation of titanium, but with no

change in the nails. In contrast other studies revealed that, there was no evidence of “yellow nails” among drug addicted patients of an anatomical studies. This is still a controversial topic which is still in debate.



Fig. 2: Yellow nail syndrome; High level of titanium in nail clippings

## 2 SUMMARY

Corrosion and abrasion from titanium implants are believed to be reason for tissue inflammation<sup>(28)</sup>. Evidence for existence of hypersensitivity or allergy against titanium consists in a limited number of cases, such reactions in tissue proximity to implant can be detected. However, less specificity as the observed reactions could be initiated by other factors associated with the placement of implants<sup>(28)</sup>.

Wang et al.<sup>(29)</sup> in mice study detected that deposition of TiO<sub>2</sub> mainly in the liver, spleen, kidneys, and lungs by ICP-MS. He further identified liver damage, spotty necrosis of hepatocytes, and swelling of glomeruli in mice. They also detected an increase in ALT/AST ratio which is an indicator of liver damage.

In a simple word, elevated concentration of metal ions may be toxic and noxious in oral cavity. Impurities occurs only if other elements get incorporated over titanium. These elemental impurities over titanium implant initiate allergic reactions both local and systemically<sup>(30)</sup>.

## 3 CONCLUSION

Titanium has more corrosion resistance, but favourable biocompatibility. Accumulations of titanium ion particles and its alloy over both peri-implant tissues and systemic, leads to toxic complications such as yellow nail syndrome, hypersensitive reaction and also inflammation over surrounding tissues. Zirconia containing implants are gaining popularity in implant world nowadays, but still some limitations are present. However long-term clinical data are also needed. Within this article limitations, it was suggested that we shall gain a sound knowledge of the rare problems of titanium toxicity and its alloy.

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