



Ana Sofia de Sousa Moreira^{1*}, Ana Patrícia Silva MAgalhães¹, Bruno Miguel Santos Carvalho¹, Juliana Cardoso Costa Santos¹, Ana Isabel Pereira Portela² and Mário Ramalho de Vasconcelos²

¹Dental Degree, Faculty of Dental Medicine, University of Porto, Portugal

²Dental Materials Department of Faculty of Dental Medicine, University of Porto, Portugal

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***Corresponding author:** Ana Sofia de Sousa Moreira, Dental Degree, Faculty of Dental Medicine, University of Porto, Rua das Agradas, 3104580-796, Lordelo – Paredes, Portugal, Tel: +351 916176122; E-mail: sofia_moreira93@hotmail.com

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Review Article

Titanium Allergy: Is Zirconia a Viable Alternative?

Abstract

Purpose: Highlight and discuss the properties of zirconia compared to titanium, in the case of titanium allergies.

Materials and methods: The research was divided into 3 themes: Titanium Allergies: clinical cases reported, with the key-words: Titanium allergy; Dental Implants, in the databases MEDLINE / PubMed, Google Scholar and the archives of the library of the Faculty of Dental Medicine, University of Porto.

Results: Dental implants are a good approach for replacement of lost teeth. Titanium and titanium alloys are the material of choice for fabrication of dental implants. However there is a possibility of allergic reactions occur. In that way, zirconia seems to be a potential alternative to titanium implants because of its biocompatibility, mechanical properties, aesthetics and low plaque affinity.

Conclusions: Zirconia dental implants have the potential to become an alternative however further clinical scientific information is needed.

Introduction

Partly or totally toothless patients have been successfully rehabilitated through the use of dental implants [1,2]. Currently, titanium and their alloys are the preferred materials for the fabrication of implants [2–9], since it is a relatively inexpensive material [9], and displays excellent biocompatibility promoting osseointegration [2,10–13]. Moreover, it has good mechanical properties [2,10,12,14], and a high corrosion resistance [14]. Despite expressing a number of disadvantages, including aesthetics, the possibility of allergic reactions does not fit in the new concept of “metal-free” [2–4,7,12,14–17]. As the titanium implants have a grey color, this can be reflected by the mucosa, or even get exposed in case of gingival recession [3,4,8,14,17–20]. Although rare, they have also been reported cases of titanium hypersensitivity [3,21–23], with the presence of typical symptoms such as eczema and itchiness leading to loss of the implant [21,24].

The pure titanium and the Ti–6Al–4V alloys are mainly used in biomedical applications and in dentistry in particular titanium alloys, aluminum and vanadium are often used instead of pure titanium due to its greater strength [25,26]. However several other elements in the alloys have been detected and these “impurities” may be responsible for initiating the allergic response [26]. The most commonly reported type of hypersensitivity is type IV, which is a delayed-type reaction

mediated by T lymphocytes with abundant macrophages and an absence of B-lymphocytes [21,26,27]. There are epidemiological studies of prevalence of specific allergy to titanium in the general population, however, since the external exposure to this metal is so important its related pathology is scarce and the cases documented in the literature are few, that is why we suspect that the prevalence is low [22]. It is also reported that cases of hypersensitivity to implants are more common in people with a history of hypersensitivity to other metals or jewelry [24].

Due to these disadvantages, some new materials have been marketed as an alternative to titanium. Ceramic based materials has the potential to become the alternative of choice because of their aesthetic properties, its color mimics the natural tooth [7,14,16,28]. The alumina (Al₂O₃) has been used as an alternative to titanium implants, however due to their insufficient physical properties, such as high fracture risk, it was withdrawn [3,4,7,17,20,29]. Subsequently, another ceramic was introduced, zirconia (ZrO₂) which adding to its biocompatible, has also a good aesthetic [3,5,10,28]. With regard to its physical and mechanical properties it presents: low corrosion, low thermal conductivity, high flexure strength (900–1200 MPa), hardness (Vickers 1200), Weibull modulus [10–12], and low propensity for the buildup of microorganisms [3,4,7,11,14,16,17,20,29,30].

This review aims to highlight and discuss the properties of zirconia compared to titanium, in the case of titanium allergies. Titanium allergy is often neglected by dental professionals because of lack of knowledge about its impact. This article draws attention to this topic. Besides that new information on dental implants is regularly published. With this article, we aim to help dental professionals, who want alternatives to titanium implants, by simplifying their research.

Material and Methods

In order to accomplish this work, it was used the databases MEDLINE / PubMed and Google Scholar, as well as the archives of the library of the Faculty of Dental Medicine, University of Porto. The search was limited to articles in English, with full text available, without the year of publication limit.

The research was divided into 3 themes. In the first theme – Titanium Allergies: clinical cases reported, with the search key-words: Titanium allergy; Dental Implants, and taking into account the inclusion factors: studies and clinical cases in humans. In the second theme – Titanium Alternatives, using the search key-words: Titanium alternatives; Dental Implants, taking into account the inclusion factors: alternatives only related to the field of dental implantology.

Results

The research results were 17 articles. After reading them all, were selected [8], according to the exclusion factor: in vitro studies. In the second theme were found 11 in total, of which, after reading them all, were selected [4], according to the following exclusion criteria: articles about substituting titanium abutments instead of titanium implants.

For the third theme – Zirconia implants as an alternative to titanium implants, using the search key-words: Titanium; Zirconia; Implants, having humans species as the only factor of inclusion, 155 articles were found, of which after reading them all, 36 were selected, according to the exclusion criteria: an abstract with no relevance to the comparison of titanium and zirconia implants.

Discussion

Titanium Allergies: clinical cases reported

Titanium allergies are well demonstrated in orthopedic

appliances with symptoms of urticaria, eczema, skin and mucosal itching and redness [22]. However it's not known if those findings can be extrapolated to the oral mucosa surrounding the implants, by two reasons: first the contact surface between bone and implant are smaller and, by other hand, oral mucosa and skin are immunologically distinct. In oral mucosa the number of Langerhans Cells presenting antigens is much lower than the skin which implies that the oral mucosa needs to be exposed to an allergenic concentration 5 to 12 times higher than the skin to induce an identical hypersensitivity reaction [22]. In this research were found many clinical reports of strange reactions to titanium implants (Table 1) whose authors suspect it may be titanium allergies [21-23,31]. Patients that are affected by metal allergens are tested clinically by the epicutaneous “patch” test or alternatively in vitro with the Lymphocyte Transformation Test (LTT) or Leukocyte Migration Inhibition Test (LMIT) [21,24,27].

Egusa et al., reports a 50 year-old woman with a 2-years history facial eczema after receiving titanium dental implants. The aim of the two implants was to place a mandibular overdenture. One week after implant removal the symptoms of the eczema worsened but therefore gradually improved with a complete remission achieved in 10 months. The authors suggested that the initial worsening of the symptoms were due to a new contact with titanium debris antigens during the implant removal surgery. The patient had an LTT positive result to titanium and this plus the medical history gave the diagnosis of titanium allergy [21].

Mitchell et al. reported two gingival hyperplasia cases. The first patient was a 61 year-old woman with a history of penicillin allergy and was taking calcium supplements and estrogen. Four mandibular implants were placed and within 2 weeks of titanium abutment connection was noted a gingival hyperplasia around all cylinders. The titanium abutments were removed and substituted by custom-fabricated gold abutment cylinders. One of the implants was no longer osseointegrated and was also removed. Histologically a high number of eosinophils around the granulation tissue were observed. The authors suspected that the steroids taken by the patient may have raised the liability to a foreign-body reaction. The second patient was a 44 year-old woman with gingival hyperplasia to titanium abutments 3,5 weeks after its placement. The

Table 1: Symptomatic Titanium Allergies Report.

Autors and year	Subjects (mean age/ range years)	Subjects with Ti allergy (%)	Gender	Number of implants placed	Duration of the implants in function	Symptoms
Egusa et al. 200821	1 (50)	1 (100%)	F	2	2 Years	2 years long Facial Eczema
Sicilia et al. 200822	35 (50,2/21-68)*	9 (0,6%)	10M 25F	INA	INA	Skin Rash, Eczema, Flush, Dermatitis and Urticaria
Mitchell et al. 199023	2 (52,5/44-61)	2 (100%)	1M 1F	4 in each patient	2 weeks (F) 3,5 months (M)	Gingival Hyperplasia
Muller et al. 200632	56 (53,8/14,8-84,1)	21 (37,5%)	17M 39F	INA	6 months	Dermatitis and acne-like facial inflammation
Du Preez et al. 200733	1 (49)	1 (100%)	F	6	1 week	Swelling in submental and lingual sulcus, pain and hyperemia of the soft tissues.

*35 selected from a total of 1500; † Symptoms of both type I hypersensitivity and type IV. Ti = Titanium; M = Male; F = Female; INA – Information Not available

resolution was also obtained by substituting the titanium abutments by custom gold abutments [23].

Sicilia et al. [22] made a clinical study with 1500 patients between 2002 and 2004, however of those only 35 patients were included. The authors observed redness, urticaria, dermatitis skin rash and facial eczema in patients with Titanium implants that fulfilled the eligibility criteria: presence of allergic symptoms after implant surgery, de-keratinized hyperplastic lesions of peri-implant soft-tissues, unexplained implant failures, history of several allergies, having undergone at least 3 implant surgeries. Of those 35 carefully-selected patients only 9 had a positive reaction to titanium after cutaneous and epicutaneous test, of which 7 presented both type I and type IV hypersensitivity reaction and only 2 patients presented pure type IV reactions.

Muller et al. in a clinical and experimental study with 56 patients reported a clinically significant allergy to titanium implants in 21 of those and observed dermatitis and acne-like facial inflammation as symptoms [32].

Du Preez et al. in their case report with just 1 subject, a 49 years-old female which had been placed 6 mandibular implants on the lower jaw, developed an allergic reaction whose symptoms were swelling in submental and labial sulcus, pain and hyperemia of soft tissues. It was observed a chronic inflammatory response with fibrosis surrounding the implants [33].

Titanium Alternatives

There was not sufficient evidence, in all the articles found, recommending a viable alternative to completely substitute titanium for another material in clinical practice. Using titanium alloys like Ti-6Al-4V or Ti-15V rather than Commercially Pure grant better physical properties [34], but in specific titanium allergy cases it does not solve the problem as titanium remains present. Ribeiro et al. studied a new TiNbZr alloy with similar characteristics to Ti-6Al-4V [35], but it also does not solve the titanium allergy issue. Zirconia implants are the only remaining titanium-free viable alternative as it is shown in Kohal et al. investigation [36]. Gold-based alloys were classically used but they promoted a fibrous interface between implant and bone [37].

In the next part of the present review, as zirconia remained the only candidate to substitute titanium implants in these patients, we decided to compare its properties against titanium (Table 2).

Zirconia implants as an alternative to titanium implants

Biocompatibility is defined as the capacity of a material to be used with an appropriate response by a human host, without any kind of allergic, inflammatory, toxic, mutagenic nor carcinogenic reactions [38]. Zirconia implants have a high biocompatibility [1,2,5,11,14,28,30,39,40], and a similar to titanium soft tissue response [7]. The inflammatory response and bone reabsorption induced by ceramic particles are less than those induced by titanium particles which suggests the

Table 2: Comparison parameters between titanium and zirconia implants.

Comparative Terms	Titanium	Zirconia
Biocompatibility	High [12-14, 25, 30, 50]	High [2, 5, 11, 12, 14, 28, 30, 39, 40]
Osteointegration	Similar [2, 3, 7, 11, 12, 14, 17, 19, 41-44]	Similar or even better [8, 10, 43]
Osteoblasts behavior	Better [41]	Worse [41]
Fibroblasts behavior	Better [31]spreading	Better [13] (alignment and proliferation)
Bacterial adhesion	Higher [8]	Lower [3, 4, 7, 8, 11, 14, 19, 30, 38, 42, 44, 46-48]
Fungal adhesion	Similar [49]	-
Stress Distribution	Lower [12]	Similar [1, 2, 7, 10, 17, 44]
Aesthetics	Lower [1, 6, 7, 11, 12, 18, 19, 30, 39]	Higher [4, 6, 7, 11, 12, 19, 28, 38-40]
Long-time success	-	Need more investigation [8, 14, 17, 20, 28]

ceramics biocompatibility [2]. All authors refer that zirconia and titanium have a similar biocompatibility.

Osseointegration is an integration interaction between implant and bone leading to implant-bone anchorage which is vital to the implant success [41]. Osseointegration is similar to zirconia and titanium implants [2,7,11,12,14,17,19,42-44], or even better [10,43]. Long-term osseointegration success is dependent of a rigorous oral hygiene in both types of dental implants and high stress distributions in the bone should be avoided as it can induce severe surrounding bone reabsorption leading to implant loosening and further complete loss of implant [7].

Implant surface is determinant to cellular adhesion⁴¹. In implants with roughened surfaces, higher forces are required to break implant-bone anchorage in comparison to smooth-surfaces implants [41]. Yamano et al. [13], investigated the cellular response of human gingival fibroblasts cultured on smooth or rough zirconia or titanium disks. The study demonstrated that smooth zirconia surface promoted more alignment and proliferation of the cells. However after 3 hours of culture smooth zirconia surface showed the weakest spreading compared to the other surfaces. Kohal et al. [41], examined the in vitro and in vivo response of osteoblasts to a novel acid-etched and sandblasted zirconia surface. The osteoblasts were cultured on electrochemically anodized titanium, machined titanium, novel zirconia surface and machined zirconia. The in vitro investigation revealed that the osteoblast behavior on the novel zirconia surface was similar to the machined surfaces (cell proliferation) and on the other hand similar to the rough titanium surface (cytoskeleton). However in the in vivo experiment the novel zirconia surface performed worse than standard titanium implant surface modification.

As the implants are exposed to saliva in the oral cavity, an acquired pellicle is formed on its surface. This pellicle acts as an interface between bacteria and the implant surface [42,45]. The presence of bacteria is the major contributor to peri-implantitis, which is an inflammatory reaction in the tissues

surrounding an osseointegrated implant in function, resulting in inflamed, swollen and bleeding of tissues resulting in alveolar bone destruction culminating in implant loss [4,8,45,46]. The bacterial adhesion is influenced by a group of factors like the physicochemical properties of the material surface such as the roughness, hydrophobicity and electric charge [8,45]. To the majority of authors bacterial adhesion is lower in zirconia than titanium [4,7,11,13,14,17,19,30,38,42,44,45,47,48]. This is probably explained by zirconia lower surface free energy [42], however to Egawa et al. initially the bacterial adhesion is similar but in zirconia implants it decreases with time. Titanium surfaces appear to be coated in a more uniform way with a structured biofilm, on the other hand zirconia surface appear colonized by clusters of bacteria [45,48].

Candida albicans is the most common fungus in oral cavity and is related to periodontal and peri-implantar lesions [49]. The attachment of *Candida albicans* is influenced by the surface roughness, which means that rough and textured dental implant surfaces have a higher fungal colonization [49]. Bürgers et al. in his study compared zirconia with three titanium implants (with different roughness) and conclude that zirconia did not show any reduced proneness to adhere to *Candida albicans* in comparison to titanium [49].

Özkurt and Kazazoglu² and Wenz et al. [29] in their literature review and Bal et al. and Chang et al. in their in vitro experiences conclude that zirconia and titanium implants have a similar stress distribution in the surrounding bone [1,7]. Mobilio et al. results are the same, but they adds that the stress level caused by zirconia implant on cortical bone is lower than that of the titanium implant [10]. However Fuh et al. found that the stress in the surrounding bone was lower for the zirconia implant [12]. The authors try to explain this with the stress shielding phenomenon (causes a reduction in the bone stress). One of the factors that influence the stress shielding is the elastic modulus that in the zirconia implants is almost double that of titanium, which means that stress will be higher adjacent to the zirconia implant and will reduce the high stresses in crestal bone near the interface [12].

One of the implant titanium disadvantages is the dark color that can shine through the peri-implant mucosa or in case of soft tissue recession [1,6,7,11,12,18–20,29,30,39,45]. Zirconia implants overcomes this disadvantages because is a white material that is similar to the natural teeth color [5–7,12,19,28,38–40].

Long time success studies on zirconia implants are still lacking [14,17,28]. However Borgonovo et al. in their two year clinical preliminary study reported an overall success rate of 95% [14]. Gahlert et al. in their retrospective clinical study cited two clinical investigations that showed success rate of 98% after one year follow-up and 95% after five years of follow-up, for zirconia implants with rough surface topographies [28].

Conclusion

Titanium has been used as a biomaterial of choice for dental implants. Since there were cases of allergy to titanium, it was necessary to do further research. Zirconia may have the potential

to be a successful implant material because it has been proved to be biocompatible in vitro and in vivo studies; it has very interesting microstructural properties, it is osteoconductive, it has a colour that match natural teeth and a low plaque affinity. However, further clinical scientific information regarding the clinical use of zirconia dental implants should be investigated.

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