The Implications of Titanium Alloys Applied in Maxillofacial Osteosynthesis

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Featured Application: The featured potential application of this article is to encourage the maxillofacial surgeons to decide which type of alloy to use for the osteosynthesis plates based on the information presented and to guide the clinicians and influence their decision regarding the necessity of removal.

Abstract: Titanium alloys are known for their biological, mechanical and chemical properties, which have successfully expanded their use in the maxillofacial field. The internal fixation using titanium miniplates and screws offer a new perspective for the treatment of trauma and in orthognathic surgery and maxillofacial oncology. Although, titanium is highly recommended for its excellent biocompatibility, recent research has focused on identifying the potential local and general implications of the interactions between the human tissue and the metallic particles. This present review aims to outline the existing tissue changes, cellular alterations and future perspectives regarding the use of titanium-based alloys as osteosynthesis materials, taking into consideration the existing present debate whether the routinely removal of these materials should be an indication.

1. Introduction

Maxillofacial fractures represent a common pathology and a continuous challenge for clinicians. Among this particular pathology, the most frequent are the mandibular fractures that imply particular attention regarding the treatment by achieving a proper functionality and aesthetic outcome through the reconstruction of the local anatomy, occlusion and functional activity [1]. Injuries in this segment include hard and soft tissue alterations that could occur from the frontal area to the mandible [2]. This region is the most exposed to trauma and the fractures can be localized at one or more bones from the maxillofacial area. The mechanism that produces the fracture, the direction and the magnitude determine the pattern and characteristics of the fracture line. The aetiology of these fractures includes a wide range of violence trauma, road traffic accidents, sport injuries, falls or work-related injuries [2,3].

1.1. Epidemiology of Maxillofacial Fractures

The maxillofacial fractures epidemiology is different based on the lifestyle, geographic area, cultural and socio-economic factors [4,5]. The statistics show that trauma in the maxillofacial area represents 35–45% from all trauma categories [6]. The fact that this type of trauma is associated with a

high morbidity rate, important aesthetic implications, severe functional alterations and a high influence upon the social life means that the maxillofacial fractures are characterized as a growing public health problem expanding worldwide [3].

The importance of understating completely the cause and the potential mechanism that produces the fracture in the facial area, as well as the severity grade and surrounding affected tissues, play an important role in deciding the proper treatment plan, the correct approach and the potential intra- and post-operative complications [7]. Research showed that the most frequent fracture in the maxillofacial area are the mandible fractures–1743 (42%), zygoma fractures (24%), orbital fractures (16%), nose fractures (9%), Le Fort fractures (5%), naso-orbito-ethmoidal fractures (1%) [3–8].

1.2. Treatment Options

Treatment of the maxillofacial fractures varies based on the type of fracture, the localization and the implication of the surrounding tissue. Studies often compare the two types of treatment options—the closed reduction and the open reduction—using rigid internal fixation, each of them presenting advantages and disadvantages [9]. A proper outcome after the treatment of the fractures in this area is based on a stable fixation with a correct reduction and reposition of the fragments, efficient fixation that offers an optimal environment for healing, remodelling and revascularization of the area [10]. The surgical approach is the primary option when the existing fracture determines severe dysfunction, disfigurement and extension of the fracture site. Furthermore, the internal bone fixation approach using miniplates and screws is recommended when the intermaxillary immobilization is difficult for the patient or it has contraindications to be performed [11]. As an election material, titanium miniplates and screws proved an asset for the surgical treatment with a high biocompatibility that quickly found its use in traumatology, orthognathic surgery and maxillofacial oncology [1].

1.3. Healing and Repairing Process

The healing process is based on the intervention of the bone tissue, the bone marrow's cells, the periosteum and the soft tissue [12]. The homeostasis of the bone tissue is kept by the interactions of the osteoblasts, osteoclasts, bone-lining cells and osteocytes, all of them being responsible for the remodelling process [13]. When an interruption in the normal process occurs due to various causes, the aim is to regain the normal function of the tissue. A special category of cells that were discovered in the bone marrow have the power to differentiate into various other cell types, and among them are osteoblasts and chondrocytes. These cells are the mesenchymal stem cells (MSC), and they are defined through several specific surface markers (CD73, CD90 and CD105) [14]. Multiple studies have been conducted and the results revealed an important characteristic of the MSC—a characteristic that offers them a crucial role in the regenerative and reparative process of several adult tissues (bone, muscles, neuronal cells). The immunomodulatory effects of the MSC as proangiogenic, prosurvival and antiapoptosis properties transform them into an important adjuvant in tissue engineering and regenerative medicine [14]. In the oral cavity, the oral-derived stem cells (ODSC) can be obtained from the extracted teeth, mainly from the fresh dental pulp. Offering such an easy approach in the oral environment, this type of mesenchymal stem cells has gained the attention of researchers for further studies [15]. Also, similar cell populations have been identified in the periodontal ligament, dental follicle and gingival tissue with remarkable regenerative potential [16–18]. Further clinical studies that examined the oral bone formation after the removal of periapical cysts, describe the implication of stem-like cells in the local regenerative process, suggesting their presence in the granulation tissue [19]. These results could influence and change the perspective of bone regeneration in the maxillofacial region after the excision of cystic pathology. Multiple studies focus on reporting the existing relationship between the mesenchymal stem cells and bone tissue regeneration. The implication of the TGFβ1 gene in the differentiation process influences the mesenchymal stem cell's pathway to either an osteogenic or adipogenic cell. The use of PRP blood clot or vitamin D associated with dental-derived mesenchymal stem cells promoted the osteogenic process in the reported studies [20]. Taking into consideration the

high potential of the oral cavity's tissues to provide mesenchymal stem cells that can develop into different types of tissue, the path of regenerative medicine encountered a new challenge. The oral mesenchymal stem cells are the target, possessing immunomodulatory molecules that have direct action upon the healing process and the inflammatory alterations.

Another possibility that promotes bone healing and regeneration in preclinical and clinical trials is the involvement of growth factors. The results revealed that for the expected results, the dose of growth factors is very high in order to accomplish the desired outcome, generating extreme cell multiplication [21]. In order to accelerate the bone regeneration, nanomaterials could be an option as the dimension is similar to the bone and the shape facilitates the local bioactivity, improving the bone growth. Several studies have revealed that a certain nanotopography of the inserted bone implants can influence bone regeneration. Also, nanomaterials can serve as matrices for the stem cells in order to obtain osteolineage, that could permit their differentiation [21]. Results have been obtained when bioactive coating of the implants occurred. Using titanium implants associated with bioactive coating proved to determine new bone growth at the interface. Nanoengineered biomaterials that target the regenerative potential of the bone tissue and promote the osteoblastic activity can be added to the implanted scaffold in order to stimulate and accelerate local healing.

Dental pulp stem cells (DPSCs) offer the change of using an autologous source in order to trigger and influence the regenerative process. The studies performed on culture cells with the association of human platelet lysate (PL) replacing the animal serum were a success. Human platelet lysate is biocompatible, generating no risk of viral transmission or contamination [22]. The dental pulp stem cells have osteogenic and angiogenic potential, with multiple differentiation possibilities. The study conducted by Marrazo et al. [22] analysed in vitro the effects that the added human platelet lysate had upon the dental pulp stem cells. The results showed a higher rate of the cell viability and proliferation when PL in concentration 1% was used, in comparison to the normal protocol that uses foetal bovine serum (FBS).

The medical procedures contribute to the solution of recreating a proper environment in order to regain the morpho-functional characteristics, to offer optimal conditions for the integration and the local remodelling process with the help of material substitutes. The term of biomedical devices refers to the replacement of the missing tissues using tested materials that can successfully fulfil all the desiderates of the specific area, maintaining a good interaction with the surrounding tissues [23], as shown in Table 1.

Table 1. Characteristics of metals used in maxillofacial reconstructions.

Property	Description
Elasticity Module	The amount of force required to break the material
Shear Stress	The amount of force required to break the material in a sliding type vector
Tensile Strength	The resistance of breaking under various tensions
Yield Strength	The amount of force required to deform the material

The osteosynthesis method in the maxillofacial field desires to regain the functionality and morphology of the bones, creating an optimal environment for the osteogenic process with the help of different materials that are biocompatible. The present review aims to evaluate the use of titanium alloys in maxillofacial osteosynthesis under various forms, the advantages and disadvantages that accompany their use and their long-term implications in relation with the surrounding tissues. Taking into consideration the important properties that titanium possesses, the existing studies still debate if the titanium alloys materials could be left or should be removed after a period of time due to possible alterations in the surrounding tissue and body fluids.

2. Titanium Alloys Used in Osteosynthesis

The medical approach regarding the pathology that regards the bone tissue by disrupting its continuity is based on the fixation of the bone segments by using various materials. Usually, titanium plates and screws contribute to the internal fixation in maxillofacial osteotomies and fractures. Among the important properties that such a material needs to possess in order to fulfil its functions are tensile strength and hardness [24]. Osteosynthesis treatment was improved once the titanium alloys were introduced as a first option materials in the maxillofacial fractures [25]. Ti-6Al-4V (TAV), Ti-GAl-7Nb (TAN) and Ti-6Al-4V ELI (TAV ELI) are the most frequently used titanium alloys in the fabrication of miniplates and various orthopaedic devices due to the fact that they possess an α and β microstructure [26], as displayed in Table 2.

Table 2. Titanium alloys used in medical field.

Pure Titanium (Grade 1,2,3,4)
Ti–6Al–4V ELI (α + β type) (titanium-4 aluminium-4 vanadium Extra-Low Interstitial) Ti-6Al-4V (α + β type) (titanium-6 aluminium-4 vanadium) Ti–6Al–7Nb (α + β type) (titanium-6 aluminium- 7 niobium)
Ti–5Al–2.5Fe (β rich, α + β type) (titanium- 5 aluminium- 2,5 iron) Ti–5Al–3Mo–4Zr (α + β type) (titanium- 5 aluminium-3 molibdem-4 zirconium) Ti–15Mo (β type) (titanium- 15 molibdem) Ti–15Mo–5Zr–3Au (β type) (titanium- 15 molibden- 5 zirconium- 3 gold) Ti–15Sn–4Nb–2Ta–0.2Pd (α + β type) (titanium- 15 stanium- 4niobium- 2 tantalum- 0,2 palladium)
Ti–15Zr–4Nb–2Ta–0.2Pd (α + β type) (titanium-15 zirconium-4 niobium-2 tantalum-0,2 palladium) Ti–15Mo–3Nb (β type) (titanium-15 molibdem-3 niobium) Ti–12Mo–6Zr–2Fe (β type) (titanium-12 molibdem-6 zirconium-2 iron) Ti–35.3Nb–5.1Ta–7.1Zr (β type) (titanium-35,3 niobium-5,1 tantalum-7,12 zirconium)

Titanium has the desired mechanical properties in order to serve as an internal rigid fixation material, taking into consideration also the fact that it is characterized by a high degree of biocompatibility [27]. The goal in the osteosynthesis treatment was to overcome all the limitations that other materials had in the past by introducing all the advantages that the titanium alloys possess [28]. Research showed that for the biocompatibility of the titanium the oxide layer that forms on its surface is responsible [28] for helping the integration process. The pure titanium can be classified into four groups based on their oxygen composition, with grade 4 containing the most amount on oxygen (0.4%) and grade 1 the least amount (0.18%) [29]. The α and β titanium alloys are the standard combination that offer excellent mechanical properties, biocompatibility and resistance to corrosion. Recently, studies have focused on the single β titanium alloys based on the fact that their process can be directed in order to modify the properties and improve the corrosion resistance, to lower the elasticity modulus and to influence the notch resistance [26].

Alloys based on titanium are classified as nontoxic materials that are popular for their good biological response [30,31], except those that have vanadium in their componence, since this material seems to have a cytotoxic potential.

Several in vivo studies conducted on animals proved the fact that although vanadium determined a cytotoxic response, the overall biocompatibility of Ti-6Al-4V alloys is similar to the ones without vanadium [32].

The surface of titanium alloys are covered in an oxide layer that confers resistance to corrosion and offers acceptable biological properties. The surface oxide films are mainly consisting of stable oxides like TiO_2, Al_2O_3, Zr_2O_5 and MoO_3. These types of oxides assure the insolubility in various biological fluids, which facilitates the biocompatibility for the titanium alloys. Research proved that Ti-15Mo and the CP titanium had the best resistance to corrosion towards a solution-based phosphate buffered saline, and Ti-6Al-7Nb and Ti-6Al-4V were the best alloy combination with remarkable corrosion and sliding wear resistance [33]. The applications of the titanium alloys are indicated by their properties,

such as fatigue strength, wear, stress resistance and corrosion resistance—properties that dictate the proper use in various clinical situations.

Bone osteosynthesis treatment uses metallic miniplates and screws that can sustain and replace all the functions of the facial bones. Titanium alloys have quickly become the best alternative that can provide a good contour of the replaced bone structure, having ideal resistance, elasticity, tensile strength and biocompatibility [33–35]. The titanium composition provides an important biocompatible characteristic that determines the activation of the osteointegration process with the apposition of bone tissue in the reconstructed area.

3. General and Local Implications of Titanium Alloys

The main target of the bone healing process near a fracture sites is based on a proper vascularization, a correct repositioning of the bone fragments and an optimal immobilization using an adequate material [36]. Currently, the most popular approach for this type of intervention are the metallic miniplates and screws, avoiding in this way the maxilla–mandibular fixation [37]. The advantages of this type of treatment include an early recovery with a functional masticatory function and an improved aesthetic outcome. Over time, studies mentioned several potential disadvantages related to their lifelong remanence in relation with the tissues, the most common being the possible sensibility disturbances [38], growth disturbances, impediments in radiotherapy irradiation [39] or situations when the miniplates become palpable [40,41].

Research outlined the fact that certain postoperative complications related to the mandible fracture surgical treatment were encountered in 20–26% of the interventions [42,43]. Multiple complications can occur after this type of treatment, of which the nonunion of the fracture site, osteomyelitis, infections and dehiscence are the most frequent [44,45]. Also, implications directly related to the titanium miniplates and screws were reported—failures related to the fracture of the miniplates or the loosening of the screws [42].

General and local implication while using titanium alloys for the osteosynthesis treatment in the maxillofacial area have been the subject of many studies, leaving an important question mark regarding their use, their potential influences upon the human body and their routinely removal.

3.1. Inducing Oxidative Stress and Cell Damage

Titanium alloys miniplates and screws have multiple advantages associated with the treatment of maxillofacial trauma, orthognathic surgery or oncological reconstructive treatment. However, several studies raise an important question regarding reported negative outcomes [46,47]. Research has investigated the hypothesis that the chronic inflammation around titanium alloys miniplates and screws can induce an increased production of reactive nitrogen species and oxygen-free radicals [48–50]. The problem associated with the activation of the reactive oxygen species and the production of reactive nitrogen ones is the damage that follows, affecting the normal cell function and influencing the production of the proinflammatory mediators with a consequence upon the growth, differentiation and apoptosis functions of the normal cells [51]. As far as it was investigated, oxidative stress is one of the inductive mechanisms of the titanium toxicity [52], but the exact amount of damage that it can produce cannot yet be quantified. A study was conducted by Borys et al. [1], being the only one that aimed to evaluate the effect that titanium alloys materials used for osteosynthesis had upon the redox balance found at the placement of the material and upon the systemic health. The results of the study showed that several of the oxidative damage products were increased in the mandibular periosteum of patients with mandibular fractures that were treated with titanium alloy osteosynthesis materials compared to the control group. The results showed that the advanced glycation end products (AGE) fluorescence was increased in the mandibular periosteum of the target group compared to the control, the advanced oxidation protein products (AOPP) and 4-HNE levels were significantly higher also in the target group. At the same time, the concentration of 8-OHdG in the target group compared to the control showed similar values [1]. In the same study, the evaluation of the antioxidant

defence mechanisms showed that the catalase (CAT) activity was lower in the mandibular periosteum of the target group and higher in the erythrocytes of the same group compared to the control one [1]. Also, the superoxide dismutase (SOD) activity showed an increased value in the evaluated group compared to the healthy one, while it showed no influence upon the erythrocytes. The uric acid (UA) concentration was higher both in the periosteum and plasma of the patients with mandibular fractures when compared to the controls [1]. These results suggest an increased imbalance of the redox homeostasis and oxidative stress management associated to the patients with mandibular fractures that were treated with titanium alloys miniplates and screws. The alterations could be identified in the periosteum nearby the titanium alloys by an increased level of lipid metabolism and oxidative protein products in comparison to the healthy control group. Several changes related to the activity of enzymatic and nonenzymatic antioxidants were also observed in the erythrocytes and plasma of the target group.

A study conducted by Wang et al. [53] outlined the fact that the released titanium ions from the materials could influence the osteoclasts and phagocytes to increase the production of reactive oxidative species and reactive nitrogen species. Through this mechanism the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity is higher, producing a large number of free radicals. The high level of reactive oxygen species can influence the beginning of an inflammatory process near the titanium material [52–55].

An imbalance in the normal redox value can determine a high production of free radicals and peroxides, causing damage upon all cell components, especially DNA. Besides local side effects, oxidative stress can be a cause for neurodegenerative conditions. Involving the oral cavity, the alterations of the small nerve fibres of the oral mucosa have been reported, inducing dysgeusia and burning pain [56]. A study conducted by Tatullo et al. [56] reveals the fact that an increased level of oxygen reactive species was identified in the study group, suggesting a direct implication in the pathogenesis of the described oral pain.

The disturbance of the redox balance and the production of excessive oxidative alterations in the cells can highly influence the remodelling process in patients treated for mandibular fractures [52,57]. What determines the perturbance of this process is the fact that the correct healing depends on the action of osteoblasts and osteoclasts, thus it is a process that is influenced by various components, especially collagen proteins [58]. Titanium based alloys are responsible for the infiltration of titanium ions and the increased production of cytokines, the activation the osteoclasts, and starting an osteolysis action [59]. Another important implication is upon the fibroblasts, as collagen type 1 synthesis is inhibited by inducing a genomic alteration [60,61].

3.2. Influence upon the Serum Metal Levels

As described, the oxide layer formed on titanium alloys materials can suffer over time, and can even be degraded by chemical or electrical corrosion [62]. This specific action can determine the formation and release of active metallic compound into the bloodstream. Although, titanium is considered as biocompatible, this possible consequence has not been yet fully investigated and the response of the human body has not been completely elucidated [63]. Research conducted by Ferguson et al. [64] outlined the fact that metal debris have been found in patients that underwent orthopaedic surgery—a fact that raised an important doubt regarding the potential unknown consequences [64]. Taking into consideration the fact that the maxillofacial field frequently used titanium-based alloys devices for various pathologies, this aspect in an important actual concern.

A study conducted by Mercuri et al. [62] included a number of 30 subjects that had implanted different titanium-based alloys devices, including miniplates and screws, for at least one year. The aim of the study was to identify if any changes existed in the metal concentration of the serum of these subjects. The results showed that in the blood of five subjects included in the study, the levels of cobalt in the serum was higher in three subjects, the level of chromium was higher in two subjects and only one subject showed a higher level of titanium and chromium.

The existence of metallic debris that are secondary to the implantation of metallic devices has gained attention in the past years. The presence of titanium, chromium, cobalt and other metallic components can play an important role in the failure of the metallic devices by negatively influencing their strength [65]. Studies showed that the contribution of monocytes by their development into osteoclasts can determine local loosening of the metallic devices [66,67].

Zaffe et al. [68] in their study used optical microscopy to examine titanium-based alloys devices that had been removed from 28 patients after they underwent maxilla-facial surgery. Their conclusion was that in the nearby connective tissue, the blood cells contained high titanium levels, and that the release of the titanium ended when bone deposits covered the titanium surfaces. Another study performed by Meningaud et al. [69] aimed to examine the surrounding soft tissue after the removal of titanium plates, and their results revealed that titanium was released into the soft tissue during the osteosynthesis procedure, but its levels remained constant and it was characterized as being inert, as shown in Table 3.

3.3. Modifications of the Surrounding Tissue

Although titanium is described as having a good acceptance, the long-term interaction between it and the surrounding tissue is still debated and unclear [70]. Taking into consideration the potential consequences, the removal of the titanium-based materials after the healing is complete is still a subject of many research topics. The release of metal in the tissue is explained to be secondary to contamination, corrosion or during the insertion or removal manoeuvres [71–73]. A study performed by Meningaud et al. [69] concluded that the metal that was released from the titanium plates used for maxillofacial osteosynthesis is associated with the surgical part of the process. And the metal that has been released during the time that the plates were in situ was a minor quantity.

Langford et al. [74] conducted a study in which they analysed the surface of retrieved titanium plates and the surrounding tissue after their removal. After the analysis, they identified deposits of silica and aluminium on the surface, suggesting that a contamination might have occurred during the manufacture process by polishing the titanium plate, through atmospheric contamination or during the autoclaving process before their intraoperatory use. Overall, the conclusions of their research pointed out the fact that the surgical manipulation and the existing defects of manufacture are a more probable source of potential metal release in the tissue [74]. Other studies also reported the existence of silica and aluminium on the titanium plates surface and in the nearby soft tissue [75–77]. The potential influence of aluminium has been reported in several studies and associated with the incidence of osteomalacia, Parkinson's and Alzheimer's diseases [78].

In their study, Armencea et al. [79] aimed to examine and quantify the microscopic changes that occur in the soft tissue that covers the titanium plates used for osteosynthesis, in order to identify any presence of metallic deposits. After examining the soft tissue samples that were in contact with the titanium plates, they concluded that in all cases, the titanium plates were covered in fibrotic tissue, without any inflammatory signs. A dark-grey pigmentation was visually observed in the majority of the samples (16 out of 20), and under microscopic examination pigmented debris were found in all the soft tissue samples [79]. Other studied presented that titanium particles can be transported with the help of the lymphatic vessels into the local lymph nodes [80]. However, Bessho et al. in their study reported also the encounter of titanium particles in the lungs, kidneys, spleen and liver [80]. Metallic particles in the adjacent soft tissue were also reported by Acero et al. [81], finding after optical microscopic examination, pigmented deposits of a dark brown colour, having intra and extracellular localization. Pigmentation of the nearby connective tissue of a black-grey colour was observed also by Nakamura et al. [82], in seven of the enrolled patients in their study. The samples were analysed, and the results showed that the pigmented deposits could be found both intracellular and extracellular, surrounded by an apparent foreign body reaction, as shown in Table 3.

Research showed that metallic particles can be transferred into the surrounding soft tissue as a result of corrosion, defect of manufacture, mechanical damage during insertion or removal, surface contamination or while in situ during a wear process [74–83].

3.4. Generating an Immuno-Inflammatory Response

Several research papers focused on the encountered immune–inflammatory response generated by the titanium plates and screws used for osteosynthesis. Existent results that suggest an association between titanium alloys and a secondary local osteolysis have gained the attention and became a concern. In relation with the area where the titanium screws and plates became loose, an analysis of the tissue sample revealed an important implication of the macrophages in the surrounding fibrous tissue [84].

In the study performed by Katou et al. [84] the aim was to investigate the immune–inflammatory response of the soft tissue surrounding the titanium-based alloys used for osteosynthesis and the potential role of the macrophage's infiltration. Their results revealed that an important layer of fibrous connective tissue was formed with a loose outer part that contained blood vessels. Near the blood vessels, an important number of macrophages-like cells that contained fine metal particles were identified. The performed immunohistochemical analysis showed that the tissue samples examined contained CD68, CD11c, CD11a, CD11b, CD8, CD4, CD54, CD62P positive cells. The identified macrophages showed alteration that induced their lysis followed by their death. The results of the research point to the existence of a mild–moderate inflammatory condition. This was the first research that outlined an immune–inflammatory response and a fibrous encapsulation near titanium miniplates.

Rae et al. [85] in a study performed on mice, reported that in case of the presence of titanium particles that were injected into the knee joint, no remarkable tissue reaction was present, although that human fibroblasts exposed to pure titanium released a certain amount lactate dehydrogenase, inducing cell alterations.

Several existent reports also suggest that the macrophages that have phagocytized titanium particles can influence the further release of immune mediators that have a direct action upon the bone resorption and the failure of the titanium devices by their secondary loosening [86–90]. Also, the macrophages release cytokines (b-FGF, IL-1, TGF-β) that stimulate the fibroblasts to produce more collagen, which subsequently contributes to the fibrous encapsulation, as shown in Table 3 [91,92].

3.5. Allergic Reactions Associated with Titanium-Based Alloys

Titanium alloys are popular for their high biocompatibility [93,94] and tolerance in relation with the human tissue. The large use in the osteosynthesis field with positive outcomes assured the titanium-based alloys a well-deserved first place in surgical reconstructive treatment. Recent studies have focused on reporting several aspects regarding cases that describe developed allergic symptomatology in relation with titanium-based alloys. One explanation could be the fact that the advancement made in materials technology produced titanium-based products with an increased quantity of titanium, sensitizing the human body.

Thomas et al. [95] published a case report regarding a patient that had developed an allergic reaction—an eczema after an osteosynthesis procedure using a titanium-based material. In this case, the patch test revealed no reactions, and only after an examination of the blood samples, the lymphocytes showed an active response towards TiO_2.

Another case report belonging to Egusa et al. [96] described the existence of a facial eczema in relation to a titanium dental implant. The patients underwent the lymphocyte transformation tests (LLT)—tests that have been newly recognized to be precise for the testing for metal sensitivity, including titanium [97–99]. The results showed a reaction towards $TiCl_3$. The removal of the implants determined the remission of the symptomatology.

Cases of titanium allergy are still rarely reported, and it is not recognized as an expected interaction. The most used titanium-based alloys consist of titanium dioxide with a major impact in reconstructive

medicine based on their multiple advantages. An increased usage of these alloys determined an inevitable exposure of the human body. Although, while the positive allergic reactions are proven to be against titanium reagents, no patient until recently has developed a positive allergic reaction to only one titanium reagent. Taking into consideration the facts, it is safe to conclude that the incidence is low in comparison to the exposure to other metals, and titanium can be considered a low risk material. Still, changes could potentially arise in the future, as the increased exposure to these types of materials alters the human body response as a consequence.

Table 3. Studies focused on titanium-based alloys and their implications.

Reference	Titanium-Based Alloys	Type of Study	Samples	Implications and Conclusions
Borys et al. [1]	Ti4Al4V	In vivo	Soft tissue sample (periosteum) Blood sample	- Increased superoxide dismutase (**SOD**) **activity** (redox biomarker) in erythrocytes in the study group compared to the control ->**increased antioxidant defence** - Increase in uric acid (**UA**) concentration both in tissue and blood of the study group compared to the control ->**increased antioxidant defence** - Increased tacrolimus (**TAC**) level in the tissue sample of the target group compared to the control ->**increased oxidant status** - decreased oxidative stress index (**OSI**) value in both blood and tissue samples of the study group in comparison to the control ->**increased oxidant status** - increase of advanced glycation end products (**AGE**) **fluorescence** in the tissue sample (periosteum) of the study group ->**oxidative damage product** - increased advanced oxidation protein products (**AOPP**) concentration in the tissue sample (periosteum) of the study group than in the control one ->**oxidative damage product** - **elevated enzymes aspartate transaminase/alanine transaminase (ALT/AST) levels** in the study group
Wang et al. [51]	TiO$_2$	In vivo	Blood sample	- **lactate dehydrogenase (LDH) and alpha-hydroxybutyrate dehydrogenase (HBDH) increased levels** in the study group compared to the control one
Yang et al. [57]	TiVaAl	In vitro	HF19 cells (that were put in contact with the alloy)	- **toxicity** and an influence upon the clonogenic survival after the interaction with the metal debris
Mercuri et al. [60]	Ti-6Al-4V	In vivo	Blood sample	- **high levels** of cobalt, chromium and titanium in the study group compared to the control one
Zaffe et al. [66]	Titanium	In vivo	Removed titanium miniplates Soft tissue sample covering the miniplates	- **high amount** of titanium in the surrounding soft tissue - erythrocyte and lymphocyte had a **higher titanium content** than the surroundings
Meningaud et al. [67]	Titanium	In vivo	Soft tissue sample	titanium levels had **large variations**, from 4–8000 µg/g, and apparently with increased concentrations in orthognathic surgery
Langford et al. [72]	Titanium	In vivo	Removed titanium miniplates	- identification of signs of **surgical damage** on the removed plates - **local contamination** with aluminium and silica - the removed plates did not show any signs of corrosion
Armencea et al. [77]	CpTi	In vivo	Removed titanium miniplates Soft tissue sample	- **lack of inflammatory signs** in the soft tissue samples - **the presence of dark-grey pigmentation** - **the presence of fibrosis** in the soft tissue in various degrees

Table 3. *Cont.*

Reference	Titanium-Based Alloys	Type of Study	Samples	Implications and Conclusions
Acero et al. [79]	Titanium	In vivo	Removed titanium miniplates Hard and soft tissue sample covering the miniplates	- a good healing of the surrounding bone (direct attachment of vital bone to the titanium miniplate) - **dark staining** of the examined soft tissue - histological signs of **fibrosis** in the examined soft tissue - **defects and irregularities** of the plates when examined using scanning electron microscope (SEM) analysis, probably due to the substance loss - macroscopically **dark pigmentation** was visible in all cases
Katou et al. [82]	Titanium	In vivo	Soft tissue sample surrounding the titanium miniplate	- the histological examination revealed the presence of **fibrous connective tissue** with macrophages-like cells that contained metal particles -presence of CD68-positive cells, CD11c-positive cells, CD11a-positive cells, CD11b-positive cells, CD4, CD8, CD62P and CD54 - the first report that outlined the **existence of an immune–inflammatory reaction**
Lalor et al. [86]	TiAlV	In vivo	Tissue sample from the interface bone–titanium plate	- all the examined sample contained metal debris and T lymphocytes (OKT11) and macrophages were present
Maloney et al. [89]	Titanium Titanium-aluminium	In vitro	Fibroblasts	- when exposed to titanium and titanium-aluminium, fibroblasts showed no increase of ion concentrations - when exposed to only titanium metallic particles, the fibroblasts showed a ruffled membrane and filopodia - when exposed to titanium–aluminium metallic debris, fibroblasts showed no modifications

4. To Remove Titanium-Based Osteosynthesis Materials or not: A Present Debate

The removal of titanium-based alloys used in maxillofacial osteosynthesis is still an open dispute. The causes that imply the use of osteosynthesis materials in maxillofacial surgery are multiple and the proper treatment targets the regain of various functions. Titanium devices are composed of titanium alloy or fully titanium that assure good biological and physical properties [100].

They have been used for rigid internal fixation and have been considered a 'gold standard' since 1978 [101]. However, sometimes complications did occur, such as infection, screw loosening, material exposure, dark staining of the local tissue, and chronic inflammation that determined the removal of the material. Still, the routinely removal of the titanium-based alloys used for osteosynthesis is a controversial matter. Several studies focused on outlining the negative influences upon the local and general health, suggesting that a new protocol regarding the management of the osteosynthesis materials should be taken into consideration. More authors consider that routine removal is mandatory in order to avoid potential implications. Katou et al. [84] concluded that a certain immune–inflammatory response was present near the titanium materials that were used in the treatment of mandibular fractures, and the metallic particles that were released had a contribution to the persistence of the inflammation. Other authors speculated a potential carcinogenic effect of the titanium materials by presenting cases of malignant tumours of the surrounding tissue [102].

The retrospective study conducted by Yu et al. [103] reviewed 2325 cases that were treated for maxillofacial fractures using titanium-based materials. Among these patients, 2162 (92.99%) did not have the titanium osteosynthesis materials removed and 163 patients had them removed for symptomatic (5.25%) and asymptomatic (1.76%) reasons. Taking into consideration that this study was based on a large number of patients and a long-term follow-up (ten years), the conclusion would be

that there is no need to routinely remove the titanium materials and the indications for removal are strictly in relation with the existence of complications. The most common encountered complications identified were infection, exposure, loosening of the screws or discomfort.

Although, the clinical performance of titanium is widely recognized, there are still questions regarding the long-term relations with the tissue and the possible consequences. The removal of titanium-based materials is indicated when complications are associated, and the asymptomatic removal is still a discussed alternative [104]. Most reports express a clear concern towards the persistence of the titanium plates and the occurrence of corrosion [74]. Several studied report the dark pigmentation of the surrounding tissue, the mechanical wear, and the mechanical disruption during the insertion manoeuvres as being accompanied by local metal release that could potentially disseminate in other organs [74,105,106].

The finite element analysis (FEA) is useful to predict the stress distribution, the possible fracture localizations based on the design, and the material of the plate [107]. The masticatory muscles generate tension and compression of the jawbone during the physiological movements. In order to perform osteosynthesis, the main concern is to assure a correct load of force and distribution of stress in the interface between bone and implant. Zielinski et al. [108] conducted an in vitro study on polyurethane mandibles that aimed to mechanically test all designs of osteosynthesis plates used for high neck condylar mandibular fractures Their results showed that the specific designed plates for this type of fractures were weaker in comparison to the use of two straight plates, and loosening of the screws occurred in the distal fragment. In conclusion, the shape of the plate is also a factor that must be considered, taking into account the muscle insertions and the generated tension.

The study that belongs to Pinto et al. [104] aimed to evaluate the microscopic structure and the chemical composition of the titanium plates and screws that were retrieved from the osteosynthesis sites. Their conclusion regarding the examination of the titanium devices plead for the therapeutic option of not removing them except in the cases with observed clinical indications, as the modifications did not affect the local tissue. Sukegawa et al. [109] concluded that the removal of titanium plates and screws used for orthognathic surgery is mainly either as a consequence of local infection or the desire of the patient. The routine plate removal is based in the fact that once the local healing is accomplished, the titanium materials could become a potential source of further complications [110] and the patients need to be aware of the necessity of a long-term follow-up. This aspect was discussed and included in the recommendation of the Strasbourg Osteosynthesis Group in 1991 [111], suggesting that once the plate accomplished its role, the removal is desired in order to avoid any possible complications.

5. Discussion

In the present review, our purpose was to identify the potential implications that titanium-based alloys used for maxillofacial osteosynthesis could have upon the local and general health. Titanium is considered, and remains to be, a good alternative to other existing materials due to its high biological acceptance, mechanical and chemical characteristics. Maxillofacial fractures represent a frequent and challenging pathology in the clinical practice, requiring adequate treatment that establishes a proper function, continuity and aesthetic outcome. Internal bone fixation that uses miniplates and screws has a high impact upon the treatment, especially in the cases that have contraindications for the orthopaedic approach [11]. Titanium alloys miniplates and screws are routinely used in the reconstructive treatment in traumatology, orthognathic surgery and maxillofacial oncology.

The advantages that the titanium-based alloy miniplates and screws used for osteosynthesis have are well-known but, the long-term impact has yet to be established. Recent research has focused on examining both the tissue surrounding the miniplates and the removed titanium materials in order to evaluate possible existing consequences. Although until recently the removal of the titanium devices has only been indicated when complications are associated with infection and exposure, the local cellular impact of the metallic particles is an actual concern [46]. Several studies reported that during the removal of the miniplates, the surrounding tissue presented a dark staining, proving the infiltration

of metallic particles [79,81,83]. Further research affirmed the fact that these titanium particles can be easily transported via the lymphatic system into the local lymph nodes [80], and even to other organs [80].

An existing local reaction was reported, and an immuno-inflammatory reaction was identified in the fibrous connective tissue deposits. Titanium was reported to induce an increased level of oxygen-free radicals, sustaining the start of an oxidative stress process. This aspect was evaluated by Borys et al. [1], outlining the existence in the examined samples with altered protective mechanisms. Allergic reactions associated with titanium-based alloys are rare, and among them facial eczema was encountered [95,96].

The insecurity towards these types of materials used in maxillofacial osteosynthesis and their persistence in relation to human tissue determined clinicians to remove them once their purpose was accomplished.

Taking into consideration the ongoing debate and implications related to the use of this type of alloy, scientists developed a new category of bioresorbable and bioactive materials as an alternative for the metal plates. Different types of bioresorbable materials such as polyglycolic acid (PGA), polylactic acid (PLLA), copolymers of PGA and PLLA, and hydroxyapatite incorporated in PLLA allow and stimulate the formation of new bone tissue, generating no mutagenic action [41]. Although their main advantage represented by the biodegradation characteristic is very appealing, the comparison studies between the two categories of materials—metallic alloys and bioresorbable—do not have enough follow-up. With higher refracture rates, weakness, and loss of implant strength, the decision of using bioresorbable materials is an important task for surgeons [39].

References

1. Borys, J.; Maciejczyk, M.; Antonowicz, B.; Kretowski, A.; Waszkiel, D.; Bortnik, P.; Czarniecka-Bargłowska, K.; Kocisz, M.; Szulimowska, J.; Czajkowski, M.; et al. Exposureto Ti4Al4V Titanium Alloy Leads to Redox Abnormalities, Oxidative Stress, and Oxidative Damage in Patients Treated for Mandible Fractures. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 3714725. [CrossRef]

2. Bataineh, A.B.; Elarabi, M.S. Changing pattern and etiology of maxillofacial fractures during the civil uprising in Western Libya. *Med. Oral Patol. Oral Cir. Bucal.* **2018**, *23*, 248–255.

3. Mijiti, A.; Ling, W.; Tuerdi, M.; Maimaiti, A.; Tuerxun, J.; Tao, Y.Z.; Saimaiti, A.; Moming, A. Epidemiological analysis of maxillofacial fractures treated at a university hospital, Xinjiang, China: A 5-year retrospective study. *J. Cranio-Maxillofac. Surg.* **2014**, *42*, 227–233. [CrossRef] [PubMed]

4. Emodi, O.; Wolff, A.; Srouji, H.; Bahouth, H.; Noy, D.; Abu El Naaj, I.; Rachmiel, A. Trend and Demographic Characteristics of Maxillofacial Fractures in Level I Trauma Center. *J. Craniofac. Surg.* **2018**, *29*, 471–475. [CrossRef] [PubMed]

5. Sbordone, C.; Barca, I.; Petrocelli, M.; Dell'Aversana Orabona, G.; Vaira, L.A.; Colangeli, W.; Cristofaro, M.G.; Giudice, M.; Giudice, A.; Cassandro, F.M.; et al. The Influence of Socioeconomic Factors on the Epidemiology of Maxillofacial Fractures in Southern Italy. *J. Craniofac. Surg.* **2018**, *29*, 2119–2123. [CrossRef]

6. Pita Neto, I.C.; Franco, J.; Junior, J.L.A.; Santana, M.D.R.; de Abreu, L.C.; Bezerra, I.M.P.; Soares, E.C.S.; de Alencar Gondim, D.G.; Rodrigues, L.M.R. Factors Associated with the Complexity of Facial Trauma. *J. Craniofac. Surg.* **2018**, *29*, 562–566. [CrossRef]

7. Boffano, P.; Roccia, F.; Zavattero, E.; Dediol, E.; Uglešić, V.; Kovačič, Ž.; Vesnaver, A.; Konstantinović, V.S.; Petrović, M.; Stephens, J.; et al. European Maxillofacial Trauma (EURMAT) project: A multicentre and prospective study. *J. Craniomaxillofac. Surg.* **2015**, *43*, 62–70. [CrossRef]

8. Allareddy, V.; Allareddy, V.; Nalliah, R.P. Epidemiology of facial fracture injuries. *J. Oral Maxillofac. Surg.* **2011**, *69*, 2613–2618. [CrossRef]

9. Fasola, A.O.; Obiechina, A.E.; Arotiba, J.T. Incidence and pattern of maxillofacial fractures in the elderly. *Int. J. Oral Maxillofac. Surg.* **2003**, *32*, 206–208. [CrossRef]

10. Van Bakelen, N.B.; Buijs, G.; Jansma, J.; De Visscher, J.; Hoppenreijs, T.; Bergsma, J.; Stegenga, B.; Bos, R. Decision-making considerations in application of biodegradable fixation systems in maxillofacial surgery—a retrospective cohort study. *J. Craniomaxillofac. Surg.* **2014**, *42*, 417–422. [CrossRef]

11. Kuriakose, M.A.; Fardy, M.; Sirikumara, M.; Patton, D.W.; Sugar, A.W. A comparative review of 266 mandibular fractures with internal fixation using rigid (AO/ASIF) plates or mini-plates. *Br. J. Oral Maxillofac. Surg.* **1996**, *34*, 315–321. [CrossRef]

12. Dimitriou, R.E.; Tsiridis, E.; Giannoudis, P.V. Current concepts of molecular aspects of bone healing. *Injury* **2005**, *36*, 1392–1404. [CrossRef] [PubMed]

13. De Oliveira, D.P.; Ottria, L.; Gargari, M.; Candotto, V.; Silvestre, F.J.; Lauritano, D. Surface modification of titanium alloys for biomedical application: From macro to nano scale. *J. Biol. Regul. Homeost. Agents* **2017**, *31*, 221–232.

14. Tatullo, M.; Codispoti, B.; Pacifici, A.; Palmieri, F.; Marrelli, M.; Pacifici, L.; Paduano, F. Potential Use of Human Periapical Cyst-Mesenchymal Stem Cells (hPCy-MSCs) as a Novel Stem Cell Source for Regenerative Medicine Applications. *Front. Cell Dev. Biol.* **2017**, *5*, 103. [CrossRef] [PubMed]

15. Tatullo, M.; Marrelli, M.; Shakesheff, K.M.; White, L.J. Dental pulp stem cells: Function, isolation and applications in regenerative medicine. *J. Tissue Eng. Regen. Med.* **2015**, *9*, 1205–1216. [CrossRef]

16. Seo, B.M.; Miura, M.; Gronthos, S.; Bartold, P.M.; Batouli, S.; Brahim, J.; Young, M.; Gehron Robey, P.; Wang, C.Y.; Shi, S. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* **2004**, *364*, 149–155. [CrossRef]

17. Morsczeck, C.; GÖtz, W.; Schierholz, J.; Zeilhofer, F.; Kuhn, U.; Mohl, C.; Sippela, C.; Hoffmanna, K.H. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biol.* **2005**, *24*, 155–165. [CrossRef]

18. Tomar, G.B.; Srivastava, R.K.; Gupta, N.; Barhanpurkar, A.P.; Pote, S.T.; Jhaveri, H.M.; Mishr, G.C.; Wani, M.R. Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. *Biochem. Biophys. Res. Commun.* **2010**, *393*, 377–383. [CrossRef]

19. Liao, J.; Al Shahrani, M.; Al-Habib, M.; Tanaka, T.; Huang, G.T. Cells isolated from inflamed periapical tissue express mesenchymal stem cell markers and are highly osteogenic. *J. Endod.* **2011**, *37*, 1217–1224. [CrossRef]

20. Ballini, A.; Scacco, S.; Coletti, D.; Pluchino, S.; Tatullo, M. Mesenchymal Stem Cells as Promoters, Enhancers, and Playmakers of the Translational Regenerative Medicine. *Stem Cells Int.* **2017**, *2017*, 3292810. [CrossRef]

21. Barry, M.; Pearce, H.; Cross, L.; Tatullo, M.; Gaharwar, A.K. Advances in Nanotechnology for the Treatment of Osteoporosis. *Curr. Osteoporos. Rep.* **2016**, *14*, 87–94. [CrossRef] [PubMed]

22. Marrazzo, P.; Paduano, F.; Palmieri, F.; Marrelli, M.; Tatull, M. Highly Efficient In Vitro Reparative Behaviour of Dental Pulp Stem Cells Cultured with Standardised Platelet Lysate Supplementation. *Stem Cells Int.* **2016**, *2016*, 7230987. [CrossRef] [PubMed]

23. Ziegenhagen, R.; Reclaru, L.; Ardelean, L.C.; Grecu, A.F. Corrosion Resistance of Stainless Steels Intended to Come into Direct or Prolonged Contact with the Skin. *Materials* **2019**, *12*, 987. [CrossRef] [PubMed]

24. Altan, A.; Damlar, I.; Şahin, O. Can Resorbable Fixation Screws Replace Titanium Fixation Screws: A Nanoindentation Study? *J. Oral Maxillofac. Surg.* **2016**, *74*, 1421.e1–1421.e5. [CrossRef] [PubMed]

25. Katou, F.; Moteg, K. Fixation of mandibular body fracture with combination of one-piece cast splint and miniplate. *Tohoku J. Exp. Med.* **1995**, *175*, 111–121. [CrossRef] [PubMed]

26. Disegi, J.A. Titanium alloys for fracture fixation implants. *Injury* **2000**, *31*, D14–D17. [CrossRef]

27. Gargari, M.; Comuzzi, L.; Bazzato, M.F.; Sivolella, S.; di Fiore, A.; Ceruso, F.M. Treatment of peri-implantitis: Description of a technique of surgical 2 detoxification of the implant. A prospective clinical case series with 3-year follow-up. *J. Oral Implantol.* **2015**, *8*, 1–11.

28. Elias, C.N.; Lima, J.H.C.; Valiev, R.; Meyers, M.A. Biomedical applications of titanium and its alloys. *J. Miner. Met. Mater. Soc.* **2008**, *60*, 46–49. [CrossRef]

29. Calcaterra, R.; Di Girolamo, M.; Mirisola, C.; Baggi, L. Effects of repeated screw tightening on implant abutment interfaces in terms of bacterial and yeast leakage in vitro: One-time abutment versus the multiscrewing technique. *Int. J. Periodontics Restor. Dent.* **2016**, *36*, 274–280. [CrossRef]

30. Davis, R.M.; Forbes Jones, R.M. Manufacturing processes for semi-finished titanium biomedical alloys. In *Medical Applications of Titanium and Its Alloys*; Brown, S.A., Lemons, J.E., Eds.; ASTM International: West Kanshohoken, PA, USA, 1996; pp. 17–29.

31. Ionescu, F.; Reclaru, L.; Ardelean, L.C.; Blatter, A. Comparative Analysis of the Corrosion Resistance of Titanium Alloys Intended to Come into Direct or Prolonged Contact with Live Tissues. *Materials* **2019**, *12*, 2841. [CrossRef]

32. Rogers, S.D.; Howie, D.W.; Graves, S.E.; Pearcy, M.J.; Haynes, D.R. In vitro human monocyte response to wear particles of titanium alloy containing vanadium or niobium. *J. Bone Joint Surg.* **1997**, *79*, 311–315. [CrossRef]

33. Khan, M.A.; Williams, R.L.; Williams, D.E. In-vitro corrosion and wear of titanium alloys in the biological environment. *Biomaterials* **1996**, *17*, 2117–2126. [CrossRef]

34. Weber, W.; Reuther, J.; Michel, C.H.; Miihling, J. Erfahrungerbei der Versorgung yon Gesichtssch~idelfrakturen mit dem Wiirzburger Titan-Miniplattensystem. *Dtsch. Z. Mund. Kiefer. GesichtsChir.* **1990**, *14*, 46–52.

35. Marsh, J.L. The use of the Wiirzburg system to facilitate fixation in facial osteotomies. *Clin. Plast. Surg.* **1989**, *16*, 49–60. [PubMed]

36. Buijs, G.J.; van Bakelen, N.B.; Jansma, J.; de Visscher, G.A.M.; Hoppenreijs, T.J.M.; Bergsma, J.E.; Stegenga, B.; Bos, R.R.M. A randomized clinical trial of biodegradable and titanium Fixation systems in Maxillofacial surgery. *J. Dent. Res.* **2012**, *91*, 299–304. [CrossRef]

37. Stoelinga, P.J. Developments in the treatment of oral and craniomaxillofacial trauma during the last five decades. *Ned. Tijdschr. Tandheelkd.* **2003**, *110*, 321–327.

38. Suuronen, R.; Pohjonen, T.; Hietanen, J.; Lindqvist, C. A 5-year in vitro and in vivo study of the biodegradation of polylactide plates. *J. Oral Maxillofac. Surg.* **1998**, *56*, 604–605. [CrossRef]

39. Gareb, B.; van Bakelen, N.B.; Buijs, G.J.; Jansma, J.; de Visscher, J.G.A.M.; Hoppenreijs, T.J.M.; Bergsma, J.E.; van Minnen, B.; Stegenga, B.; Bos, R.R.M. Comparison of the long-term clinical performance of a biodegradable and a titanium fixation system in maxillofacial surgery: A multicenter randomized controlled trial. *PLoS ONE* **2017**, *12*, e0177152. [CrossRef]

40. Hernandez Rosa, J.; Villanueva, N.L.; Sanati-Mehrizy, P.; Factor, S.H.; Taub, P.J. Review of Maxillofacial Hardware Complications and Indications for Salvage. *Craniomaxillofac. Trauma Reconstr.* **2016**, *9*, 134–140. [CrossRef]

41. Kanno, T.; Sukegawa, S.; Furuki, Y.; Nariai, Y.; Sekine, J. Overview of innovative advances in bioresorbable plate systems for oral and maxillofacial surgery. *Jpn. Dent. Sci. Rev.* **2018**, *54*, 127–138. [CrossRef]

42. Gutta, R.; Tracy, K.; Johnson, C.; James, L.E.; Krishnan, D.G.; Marciani, R.D. Outcomes of mandible fracture treatment at an academic tertiary hospital: A 5-year analysis. *J. Oral Maxillofac. Surg.* **2014**, *72*, 550–558. [CrossRef]

43. Lucca, M.; Shastri, K.; McKenzie, W.; Kraus, J.; Finkelman, M.; Wein, R. Comparison of treatment outcomes associated with early versus late treatment of mandible fractures: A retrospective chart review and analysis. *J. Oral Maxillofac. Surg.* **2010**, *68*, 2484–2488. [CrossRef] [PubMed]

44. Batbayar, E.O.; Dijkstra, P.U.; Bos, R.R.M.; van Minnen, B. Complications of lockingand non-locking plate systems in mandibular fractures. *Int. J. Oral Maxillofac. Surg.* **2019**, *48*, 1213–1226. [CrossRef] [PubMed]

45. Mathog, R.H.; Toma, V.; Clayman, L.; Wolf, S. Nonunion of the mandible: An analysis of contributing factors. *J. Oral Maxillofac. Surg.* **2000**, *58*, 746–752. [CrossRef] [PubMed]

46. O'Connell, J.; Murphy, C.; Ikeagwuani, O.; Adley, C.; Kearns, G. The fate of titanium miniplates and screws used in maxillofacial surgery: A 10 year retrospective study. *Int. J. Oral Maxillofac. Surg.* **2009**, *38*, 731–735. [CrossRef]

47. Yamamoto, K.; Matsusue, Y.; Horita, S.; Murakami, K.; Sugiura, T. Routine removal of the plate after surgical treatment for mandibular angle fracture with a third molar in relation to the fracture line. *Ann. Maxillofac. Surg.* **2015**, *5*, 77–81. [CrossRef]

48. Borys, J.; Maciejczyk, M.; Krętowski, A.J.; Antonowicz, B.; Ratajczak-Wrona, W.; Jabłońska, E.; Załęski, P.; Waszkiel, D.; Ładny, J.R.; Żukowski, P.; et al. The redox balance in erythrocytes, plasma, and periosteum of patients with titanium fixation of the jaw. *Front. Physiol.* **2017**, *8*, 386. [CrossRef]

49. Peters, K.; Unger, R.E.; Gatti, A.M.; Sabbioni, E.; Tsaryk, R.; Kirkpatrick, C.J. Metallic nanoparticles exhibit paradoxical effects on oxidative stress and pro-inflammatory response in endothelial cells in vitro. *Int. J. Immunopathol. Pharmacol.* **2007**, *20*, 685–695. [CrossRef]

50. Olmedo, D.G.; Tasat, D.R.; Evelson, P.; Guglielmotti, M.B.; Cabrini, R.L. Biological response of tissues with macrophagic activity to titanium dioxide. *J. Biomed. Mater. Res. A* **2008**, *84*, 1087–1093. [CrossRef]

51. Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.D.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.* **2007**, *39*, 44–84. [CrossRef]

52. Tsaryk, R.; Kalbacova, M.; Hempel, U.; Scharnweber, D.; Unger, R.E.; Dieter, P.; Kirkpatrick, C.J.; Peters, K. Response of human endothelial cells to oxidative stress on Ti6Al4V alloy. *Biomaterials* **2007**, *28*, 806–813. [CrossRef] [PubMed]

53. Wang, J.; Zhou, G.; Chenetal, C. Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. *Toxicol. Lett.* **2007**, *168*, 176–185. [CrossRef] [PubMed]

54. Federico, A.; Morgillo, F.; Tuccillo, C.; Ciardiello, F.; Loguercio, C. Chronic inflammation and oxidative stress in human carcinogenesis. *Int. J. Cancer* **2007**, *121*, 2381–2386. [CrossRef] [PubMed]

55. Kalbacova, M.; Roessler, S.; Hempel, U.; Tsaryk, R.; Peters, K.; Scharnweber, D.; Kirkpatrick, J.C.; Dieter, P. The effect of electrochemically simulated titanium cathodic corrosion products on ROS production and metabolic activity of osteoblasts and monocytes/macrophages. *Biomaterials* **2007**, *28*, 3263–3272. [CrossRef] [PubMed]

56. Tatullo, M.; Marrelli, M.; Scacco, S.; Lorusso, M.; D'oria, S.; Sabatini, R.; Auteri, P.; Cagiano, R.; Inchingolo, F. Relationship between oxidative stress and "burning mouth syndrome" in female patients: A scientific hypothesis. *Eur. Rev. Med. Pharmacol. Sci.* **2012**, *16*, 1218–1221. [PubMed]

57. Wauquier, F.; Leotoing, L.; Coxam, V.; Guicheux, J.; Wittrant, Y. Oxidative stress in bone remodelling and disease. *Trends Mol. Med.* **2009**, *15*, 468–477. [CrossRef]

58. Borys, J.; Grabowska, S.Z.; Antonowicz, B.; Dryl, D.; Citko, A.; Rogowski, F. Collagentype I and III metabolism in assessment of mandible fractures healing. *Roczniki Akademii Medycznej w Bialymstoku* **2004**, *49*, 237–245.

59. Yang, S.Y.; Wu, B.; Mayton, L.; Mukherjee, P.; Robbins, P.D.; Evans, C.H.; Wooley, P.H. Protective effects of IL-1Ra or vIL-10 gene transfer on a murine model of wear debris-induced osteolysis. *Gene Ther.* **2004**, *11*, 483–491. [CrossRef]

60. Coen, N.; Kadhim, M.A.; Wright, E.G.; Case, C.P.; Mothersill, C.E. Particulate debris from a titanium metal prosthesis induces genomic instability in primary human fibroblastcells. *Br. J. Cancer* **2003**, *88*, 548–552. [CrossRef]

61. Vermes, C.; Chandrasekaran, R.; Jacobs, J.J.; Galante, J.O.; Roebuck, K.A.; Glant, T.T. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. *J. Bone Joint Surg. Am.* **2001**, *83*, 201–211. [CrossRef]

62. Mercuri, L.G.; Miloro, M.; Skipor, A.K.; Bijukumar, D.; Sukotjo, C.; Mathew, M.T. Serum Metal Levels in Maxillofacial Reconstructive Surgery Patients: A Pilot Study. *J. Oral Maxillofac. Surg.* **2018**. [CrossRef] [PubMed]

63. Jacobs, J.J.; Skipor, A.K.; Black, J.; Urban, R.; Galante, J.O. Release and excretion of metal in patients who have a total hip-replacement component made of a titanium-base alloy. *J. Bone Joint Surg. Am.* **1991**, *74*, 1475–1486. [CrossRef]

64. Ferguson, A.B., Jr.; Laing, P.G.; Hodge, E.S. The ionization of metal implants in living tissues. *J. Bone Joint Surg. Am.* **1960**, *42*, 77–90. [CrossRef] [PubMed]

65. Matusiewicz, H. Potential release of in vivo trace metals from metallic medical implants in the human body: From ions to nanoparticles-a systematic analytical review. *Acta Biomater.* **2014**, *10*, 2379–2403. [CrossRef]

66. Cadosch, D.; Al-Mushaiqri, M.S.; Gautschi, O.P.; Meagher, J.; Simmen, H.P.; Filgueira, L. Biocorrosion and uptake of titanium by human osteoclasts. *J. Biomed. Mater. Res. A* **2010**, *95*, 1004–1010. [CrossRef]

67. Cadosch, D.; Chan, E.; Gautschi, O.P.; Meagher, J.; Zellweger, R.; Filgueira, L. Titanium IV ions induced human osteoclast differentiation and enhanced bone resorption in vitro. *J. Biomed. Mater. Res. A* **2009**, *91*, 29–36. [CrossRef]

68. Zaffe, D.; Bertoldi, C.; Consolo, U. Element release from titanium devices used in oral and maxillofacial surgery. *Biomaterials* **2003**, *24*, 1093–1099. [CrossRef]

69. Meningaud, J.P.; Poupon, J.C.; Chenevier, C.; Galliot-Guilley, M.; Guibert, F. Dynamic study about metal release from titanium miniplates in maxillofacial surgery. *Int. J. Oral Maxillofac. Surg.* **2001**, *30*, 185–188. [CrossRef]

70. Langford, R.J.; Frame, J.W. Tissue changes adjacent to titanium plates in patients. *J. Cranio Maxillofac. Surg.* **2002**, *30*, 103–107. [CrossRef]

71. Ray, M.S.; Matthew, I.R.; Frame, J.W. Metallic fragments on the surface of miniplates and screws before insertion. *Br. J. Oral Maxillofac. Surg.* **1998**, *37*, 14–18. [CrossRef]

72. Schliephake, H.; Lehmann, H.; Kunz, U.; Schmelzeisen, R. Ultrastructural findings in soft tissues adjacent to titanium miniplates used in jaw fracture treatment. *Int. J. Oral Maxillofac. Surg.* **1993**, *22*, 20–25. [CrossRef]

73. Torgersen, S.; Gjerdet, N.R.; Erichsen, E.S.; Bang, G. Metal particles and tissue changes adjacent to miniplates—a retrieval study. *Acta Odontol. Scand.* **1995**, *53*, 65–71. [CrossRef]

74. Langford, R.J.; Frame, J.W. Surface analysis of titanium maxillofacial plates and screws retrieved from patients. *Int. J. Oral Maxillofac. Surg.* **2002**, *31*, 511–518. [CrossRef]

75. Matthew, I.R.; Frame, J.W.; Browne, R.M.; Millar, B.G. In vivo surface analysis of titanium and stainless steel miniplates and screws. *Int. J. Oral Maxillofac. Surg.* **1996**, *25*, 463–468. [CrossRef]

76. Moberg, L.E.; Nordenram, A.; Kjellman, O. Metal release from plates used in jaw fracture treatment. *Int. J. Oral Maxillofac. Surg.* **1989**, *18*, 311–314. [CrossRef]

77. Torgersen, S.; Gjerdet, N.R. Retrieval studies of stainless steel and titanium miniplates and screws used in maxillofacial surgery. *J. Mater Sci. Mater. Med.* **1994**, *5*, 256–262. [CrossRef]

78. Exley, C.; Birchall, J.D. The cellular toxicity of aluminium. *J. Theor. Biol.* **1992**, *159*, 83–98. [CrossRef]

79. Armencea, G.; Gheban, D.; Onisor, F.; Mitre, I.; Manea, A.; Trombitas, V.; Lazar, M.; Baciut, G.; Baciut, M.; Bran, S. Histological Change in Soft Tissue Surrounding Titanium Plates after Jaw Surgery. *Materials* **2019**, *12*, 3205. [CrossRef] [PubMed]

80. Bessho, K.; Fujimura, K.; Iizuka, T. Experimental longterm study of titanium ions eluted from pure titanium miniplates. *J. Biomed. Mater. Res.* **1995**, *29*, 901–904. [CrossRef]

81. Acero, J.; Calderon, J.; Salmeron, J.I.; Verdaguer, J.J.; Concejo, C.; Somacarrera, M.L. The behaviour of titanium as a biomaterial: Microscopy study of plates and surrounding tissues in facial osteosynthesis. *J. Craniomaxillofac. Surg.* **1999**, *27*, 117–123. [CrossRef]

82. Nakamura, S.; Takenoshita, V.; Oka, M. Complications of Miniplate Osteosynthesis for Mandibular Fractures. *J. Oral Maxillofac. Surg.* **1994**, *52*, 233–238. [CrossRef]

83. Wang, C.; Zhang, G.; Li, Z.; Zeng, X.; Xu, Y.; Zhao, S.; Hu, H.; Zhang, Y.; Ren, T. Tribological behavior of Ti-6Al-4V against cortical bone in different biolubricants. *J. Mech. Behav. Biomed. Mater.* **2019**, *90*, 460–471. [CrossRef] [PubMed]

84. 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. [CrossRef]

85. Rae, T. The biological response to titanium and titanium- aluminium-vanadium alloy particles. Long-term animal studies. *Biomaterials* **1986**, *7*, 37–40. [CrossRef]

86. Santavirta, S.; Konttinen, Y.T.; Hoikka, V.; Eskola, A. Immunopathological response to loose cement less acetabular components. *J. Bone Joint Surg.* **1991**, *73*, 38–42. [CrossRef]

87. Haynes, D.R.; Rogers, S.D.; Hay, S.; Pearey, M.J.; Howie, D.W. The difference in toxicity and release of bone-resorbing mediators induced by titanium and cobalt-chromium-alloy wear particles. *J. Bone Joint Surg.* **1993**, *75*, 825–834. [CrossRef]

88. Lalor, P.A.; Revell, P.A. T-lymphocytes and titanium aluminium vanadium (TiA1V) alloy: Evidence for immunological events associated with debris deposition. *Clin. Mater.* **1993**, *12*, 57–62. [CrossRef]

89. Kim, K.J.; Chiba, J.; Rubash, H.E. In vivo and in vitro analysis of membranes from hip prostheses inserted without cement. *J. Bone Joint Surg.* **1994**, *76*, 172–180. [CrossRef]

90. Saffar, N.A.L.; Revell, P.A. Interleukin-1 production by activated macrophages surrounding loosened orthopaedic implants: A potential role in osteolysis. *Br. J. Rheumatol.* **1994**, *33*, 309–316. [CrossRef]

91. Maloney, W.J.; Smith, R.L.; Castro, F.; Sehurman, J. Fibroblast response to metallic debris in vitro. *J. Bone Joint Surg.* **1993**, *75*, 835–844. [CrossRef]

92. Li, W.; Kumar, K.; O'Grady, R.; Velan, G.M. Role of lymphocytes in silicosis: Regulation of macrophage-derived mitogenic activity for fibroblasts. *Int. J. Exp. Pathol.* **1992**, *73*, 793–800. [PubMed]

93. Garau, V.; Masala, M.G.; Cortis, M.C.; Pittau, R. Contact stomatitis due to palladium in dental alloys: A clinical report. *J. Prosthet. Dent.* **2005**, *93*, 318–320. [CrossRef] [PubMed]

94. Hensten-Pettersen, A. Casting alloys: Side-effects. *Adv. Dent. Res.* **1992**, *6*, 38–43. [CrossRef] [PubMed]

95. Thomas, P.; Bandl, W.D.; 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 Dermat.* **2006**, *55*, 199–202. [CrossRef] [PubMed]

96. 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. [CrossRef]

97. Valentine-Thon, E.; Schiwara, H.W. Validity of MELISA for metal sensitivity testing. *Neuro Endocrinol. Lett.* **2003**, *24*, 57–64.

98. Müller, K.E.; Valentine-Thon, E. Hypersensitivity to titanium: Clinical and laboratory evidence. *Neuro Endocrinol. Lett.* **2006**, *27*, 31–35.

99. Valentine-Thon, E.; Müller, K.; Guzzi, G.; Kreisel, S.; Ohnsorge, P.; Sandkamp, M. LTTM ELISA is clinically relevant for detecting and monitoring metal sensitivity. *Neuro Endocrinol. Lett.* **2006**, *27*, 17–24.

100. Reclaru, L.; Ardelean, L.C.; Grecu, A.F.; Miu, C.A. Multicomponent Alloys for Biomedical Applications. *Eng. Steels High Entropy Alloy.* 2019. [CrossRef]

101. Champy, M.; Lodde, J.P.; Schmitt, R.; Jaeger, J.H.; Muster, D. Mandibular osteosynthesis by miniature screwed plates via a buccal approach. *J. Maxillofac. Surg.* **1978**, *6*, 14–21. [CrossRef]

102. Friedman, K.E.; Vernon, S.E. Squamous cell carcinoma developing in conjunction with a mandibular staple bone plate. *J. Oral Maxillofac. Surg.* **1983**, *41*, 265–266. [CrossRef]

103. Yu, Y.; Liu, W.; Chen, J.; Quan, L.; Zheng, X.; Liu, L. No need to routinely remove titanium implants for maxillofacial fractures. *J. Oral Maxillofac. Surg.* **2018**. [CrossRef] [PubMed]

104. Pinto, C.M.; Asprino, L.; de Moraes, M. Chemical and structural analyses of titanium plates retrieved from patients. *Int. J. Oral Maxillofac. Surg.* **2015**, *44*, 1005–1009. [CrossRef] [PubMed]

105. Thomas, P.; Iglhaut, G.; Wollenberg, A.; Cadosch, D.; Summer, B. Allergy or tolerance: Reduced inflammatory cytokine response and concomitant IL-10 production of lymphocytes and monocytes in symptom-free titanium dental implant patients. *BioMed Res. Int.* **2013**, *2013*, 539834. [CrossRef]

106. Theologie-Lygidakis, N.; Iatro, I.; Eliades, G.; Papanikolaou, S. A retrieval study on morphological and chemical changes of titanium osteosynthesis plates and adjacent tissues. *J. Craniomaxillofac. Surg.* **2007**, *35*, 168–176. [CrossRef]

107. Wang, H.; Ji, B.; Jiang, W.; Liu, L.; Zhang, P.; Tang, W.; Tian, W.; Fan, Y. Three-dimensional finite element analysis of mechanical stress in symphyseal fractured human mandible reduced with miniplates during mastication. *J. Oral Maxillofac. Surg.* **2010**, *68*, 1585–1592. [CrossRef]

108. Zieliński, R.; Kozakiewicz, M.; Konieczny, B.; Krasowski, M.; Okulski, J. Mechanical Evaluation of Titanium Plates for Osteoesynthesis High Neck Condylar Fracture of Mandible. *Materials* **2020**, *13*, 592. [CrossRef]

109. Sukegawa, S.; Kanno, T.; Manabe, Y.; Matsumoto, K.; Sukegawa-Takahashi, Y.; Masui, M.; Furuki, Y. Is the removal of osteosynthesis plates after orthognathic surgery necessary? Retrospective long-termfollow-up study. *Int. J. Oral Maxillofac. Surg.* **2018**, *47*, 1581–1586. [CrossRef]

110. Bhatt, V.; Chhabra, P.; Dover, M.S. Removal of miniplates in maxillofacial surgery: A follow-up study. *J. Oral Maxillofac. Surg.* **2005**, *63*, 756–760. [CrossRef]

111. Strasbourg Osteosynthesis Group. Consensus Statement. In Proceedings of the 3rd SORG Meeting, Volendam, The Netherlands, 14–16 November 1991.