Pertanika J. Sci. & Technol. 27 (1): 459 - 472 (2019)

PERTANIKA JOURNALS

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

Review article

Titanium and Titanium Based Alloys as Metallic Biomaterials in Medical Applications – Spine Implant Case Study

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ABSTRACT

Titanium (Ti) and Ti-based alloys presence the most widely applied as advanced biomaterials in biomedical implant applications. Moreover, these alloys are known to be the most valuable metallic materials including spinal cord surgical treatment. It becomes an interest due to its advantages compared to others, including its bio compatibility and corrosion resistant. However, an issue arises when it comes for permanent implant application as the alloy has a possible toxic effect produced from chemical reaction between body fluid environments with alloys chemical compositions. It also relies on the performance of neighbouring bone tissue to integrate with the implant surface. Abnormalities usually happen when surrounding tissue shows poor responses and rejection of implants that would leads to body inflammation. These cause an increase in foreign body reaction leading to severe body tissue response and thus, loosening of the implant. Corrosion effects and biocompatibility behaviour of implantation usage also become one of the reasons of implant damage. Here, this paper reviews the importance of using Ti and Ti-based alloys in biomedical implantation, especially in orthopaedic spinal cord injury. It also reviews the basic aspects of corrosion effects that lead to implant mechanical damage, poor response of body rejection and biocompatibility behaviour of implantation usage.

Keywords: Bacterial infection, corrosion, mechanical damage, metal discolouration, metal hypersensitivity

ARTICLE INFO

Article history:
Received: 05 April 2018
Accepted: 11 June 2018
Published: 24 January 2019

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INTRODUCTION

Several of materials including metals which have appropriate physical properties and biocompatibility are selected for biomaterials fabrication. Common metallic materials used in medical applications such as cobalt based alloys, austenitic stainless

ISSN: 0128-7680
e-ISSN: 2231-8526

steel, titanium and titanium based alloys and magnesium based alloys (Adzali et al., 2012). Titanium (Ti) and Ti-based alloys act as the newest metallic biomaterials that widely used in medical and dental territories. These alloys have displayed successful achievements as biomedical instruments (Elias et al., 2008). In medicine, widely applications were found for implant instrumentation which can substitute failed hard tissue for example, artificial hip and knee joints, fracture fixation screws, bone plates and artificial hearts. Moreover, in dentistry metallic materials are widely used as implants in oral surgery to replace single or an array of teeth or in dental prosthesis (Mary & Rajendran, 2012).

In medical applications, Ti and Ti-based alloys are intended to be the most excellence biocompatible metallic materials since its surface properties result in the spontaneous build-up oxide layer which protects the metal's surface. It is said as biocompatible materials because of its physical properties such as low level of electronic conductivity, good corrosion resistance, thermodynamic state at physiological pH values, and also because of low-ion-formation tendency in aqueous environment (Elias et al., 2008). Hence, these alloys are used for reconstructive bone and teeth.

However, in spite of its advantages, the development of human implants with respect to corrosion resistance becomes vital in medical applications. As well known, human body environment presents a corrosive medium for various implant materials which include a highly oxygenated saline electrolyte at a pH of around 7.4, body temperature of 37^{o}C, containing water, dissolved oxygen, sodium, chloride, bicarbonate, calcium, potassium, magnesium, phosphate, saliva, and various organic compounds. Moreover, bacteria exist in the human body also influence the corrosion behavior of implant materials. When it is infected, it can create an imbalance in the electrochemical equilibrium.

Here, this review focuses on electrochemical corrosion phenomena in alloys used for orthopaedic implants and also the importance of using Ti and Ti-based alloys in biomedical implantation, especially in orthopaedic spinal cord injury. It also reviews the basic aspects of corrosion effects that lead to implant mechanical damage, poor response of body rejection and biocompatibility behaviour of implantation usage of one real case study. Hence, in future this study will become a basic directions focusing on biomaterials research and development with regard to corrosion processes that need to be considered to answer the possible corrosion mechanism concern.

TI AND TI-BASED ALLOYS IMPLANT PROPERTIES

In medical application, pure Ti and low interstitial Ti-6Al-4V are commercially used as accepted Ti-base implant biomaterials (Findik, 2017). These alloys are categorized as biologically inert biomaterials. In addition, these materials presents good reactions with human body and was found tolerated well with human tissues. Instead of that its physical

properties such as high biocompatibility, specific strength, high corrosion resistance, long fatigue life, nontoxic and allergy-free elements make them suitable for implantation used materials (Niinomi & Nakai, 2011). Ti alloys are known as stable beta alloys. This type of alloy shows no second phase precipitation formation during long-time thermal exposure. The microstructures were controlled to optimize its mechanical properties essentially as ductility, strength, fatigue resistance and fracture toughness (Bhola et al., 2011).

Elemental composition of Ti and Ti-based alloys acts as a valuable role in deciding the biomaterials physical properties. One of the essential element is Vanadium which presence as an important element, on the other hand it is categorized in the toxic group. Instead of that, titanium, zirconium, niobium and tantalum present superior biocompatibility properties and was found to be in the loose connective vascularized group such as in tissue reaction (Okazaki & Gotoh, 2002). Patrascu et al., (2014) reported that titanium did not react with organic-metallic compound, it was toxic, or if they were produced, the organic-metallic were doubtful and unstable.

Ti and Ti-based alloys is said to be biocompatible to human body is mainly for the sake of the oxide film formation such as TiO_2 over its outer surface. The development of this oxide performs a strong and stable layer which spontaneously grows when it is in contact with air. The layer avoids the diffusion of the oxygen from the environment which contribute to the corrosion degradation (de Viteri & Fuentes, 2013). Instead of its superficial properties, Ti-based alloys for example, Ti6Al4V also have some disadvantages such as low elastic modulus, and has low wear resistance and it shows to have problem in articulations surfaces. It was found that Vanadium shows potential cytotoxicity and adverse tissue reactions. On the other hand, Al was found to cause long-term Alzheimer diseases (Oldani & Dominguez, 2012). When Ti implant that contains vanadium shows critical response, the releasing of vanadium ions in the body would lead to severe damages especially to the respiratory system and the blood plaquettes producing systems. By replacing V with Nb, the harmful effects to the human body can be tolerated (Nouri et al, 2010).

As investigated by Maehara et al., (2002) two types of vanadium-free Ti alloy were used to develop an artificial hip joints which are Ti-15Mo-5Zr-3Al and Ti-6Al-2Nb-1Ta-0.8Mo alloys. Both alloys were chosen because of its high fatigue strength and its low elastic modulus.

BIOCOMPATIBILITY BEHAVIOR

Biocompatibility is an important concept and vital characteristic of material to which related with living organism compatibility in implantation process. It must be accepted by body without causing any critical response including unwanted effects and also damages including chemically nor mechanically (Patrascu et al., 2014).

It is also substantial to note that mechanical properties such as the Young's modulus, tensile strength, ductility, fatigue life, fretting fatigue life, wear properties, and functionalities show significant effects to the implant performance. It should be tolerated and keep the level under controlled so that their levels are acceptable for structural biomaterials used in hard tissue implantation (Niinomi, 2003). These mechanical biocompatibility properties were found to be an essential factor for long term usage of implantation. It must also be safe, reliable, economic and physiologically acceptable to human body.

Kirmanidou et al. (2016) investigated that, the percentage of survival rates of dental and orthopaedic implants was found at satisfactory level. In dentistry, medical implants the range is from 90 to 96.5%. Meanwhile, in orthopaedic implants it shows 80-94% at 15 years for total hip arthroplasty, and the range of 98.4 – 98.7% was found at 10 years specifically in total knee prosthesis implantation. Moreover, the range of 91% was found at 10 years for shoulder arthroplasty, and 53% and 90% at 5 years for total elbow arthroplasty for patients with posttraumatic arthritis or fractures and having inflammatory arthritis. It is not biocompatible to human body if the implants are infected, fractured, and having wear of the articulating surfaces. Instead of that, patients may also diagnose with implant loosening. Commonly, this implant failure consistently relates with stress-shielding effect, septic or aseptic inflammation, fatigue and excessive activity by patient's movement which include de-bonding at the tissue-implant interface (Kirmanidou et al., 2016). It was found by Maehara et al. (2002) that both Ti-15Mo-5Zr-3Al and Ti-6Al-2Nb-1Ta-0.8Mo alloys, which are vanadium-free alloys are clear from toxicity test.

Thus, it is necessary to categorize whether the implant usage biocompatible or not when it interacts which enable them to function inside the human body. As studied previously by Patrascu et al. (2014), Kirmanidou et al. (2016), Maehara et al. (2002), Niinomi (2003), Niinomi and Nakai (2011), and Akahori et al. (2004), they presented and stressed out the importance of biocompatibility behaviour of implant usage which determine whether the material suitable for biomedical implant applications that include bio-adhesion, bio-functionality and corrosion resistance. Although the review has been limited to the study of titanium and its alloys because this metal whose widespread use has been limited by its high cost. Furthermore, Ti and Ti-alloys is considered to be biocompatible because it has low electrical conductivity which contributes to the electrochemical oxidation of Ti leading to the formation of a thin passive layer (Sidambe, 2014).

In order to that, Ti and Ti-alloy is an ideal implant material that is said to be compatible with human body if no adverse tissue response recorded. Still, it is difficult to combine all these properties if body rejection occurred because each human bodies show different rejection and responses. Some metal can be tolerated and some metals can only be tolerated in small amounts even as metallic ions. The consequences of this issue focused on corrosion of the implant material which will weaken the implant and harmful to the surrounding

tissues and organs of human body. Thus, due to complex human body surroundings, it can be said that different body responses show different compatibility behaviour of implant material.

CORROSION ACCELERATED MECHANICAL DAMAGE AND BACTERIAL INFECTION

One of the failure causes of metallic biomaterials is corrosion. This destructive attack mostly occurred on metal surface by chemical or electrochemical reaction with its surroundings (Souza et al., 2015). In this scope, implants are exposed to the corrosive environment and it is focusing on human body fluid environment. Most of the implants are permanent and thus it is exposed to human body environment for a certain or long period of time. Human body fluids are liquids that originating from inside the living humans including fluids that are excreted or secreted from the body. In other words, it consist of human blood, body fluids and other body tissues which identified as vehicles for human disease transmission of transportation (Mary & Rajendran, 2012). Moreover, human body's tissue fluid comprised of water, dissolved oxygen, proteins and various ions for example, chloride and hydroxide. In other words, human body is very aggressive environment for metal used for implantation and it is an important aspects of its biocompatibility reasons (Muslim & Abbas, 2015). Hence, it is a complex environment that is different from one human body to another.

Mary and Rajendran (2012) reported that Ti and its alloys had significant properties that were caused by passive films. The films were rapidly formed in the body fluid environment. They also stated that the corrosion of Ti was suppressed in solutions containing fluoride and eugenol. Well established surface oxide film formed on Ti protects the surface from degradation. When the surface oxide film is disorganized, the corrosion would continue and metal ions are released progressively unless the film is regenerated. The time taken for repassivation which is also termed as regeneration time is different for various materials used. It was studied that regeneration time for Ti-6Al-4V is shorter compared to stainless steel. Moreover, the repassivation rate of Ti in Hank's solution is found to be slower than that in saline and remains uninfluenced by the pH of the solution (Geetha et al., 2009). Maehara et al. (2002) found that the corrosion resistance of vanadium-free alloys which were Ti-15Mo-5Zr-3Al and Ti-6Al-2Nb-1Ta-0.8Mo alloys was as high as commercial pure Ti and Ti-6Al-4V. In addition, they found that these alloys were stable in the living human body. Prominently, an implant failure in the form of aseptic loosening may result forming metal ions in the form of wear debris or electrochemical products generated during corrosion such as Ti^{4+}, Co^{2+} and Al^{3+}. These metal ions have been reported to decrease DNA synthesis, mitochondrial dehydrogenase activity, mineralization and mRNA expression of alkaline phosphatase and osteocalcin in ROS 17/2.5 cells (Gitten et al., 2011).

As reported by Findik (2017), the discharge of non-compatible metal ions from implants bio materials into the body was mainly because of the low corrosion and wear resistance in human body fluid. It caused allergic and toxic response where it is crucial to human structure. An interaction between the implant material and chemical compound induced by electrochemical reaction may leads to mechanical and biological complications. Mechanical complication accelerated by corrosion usually results in fatigue fracture. Meanwhile, biological complications related to corrosion could cause toxicity, carcinogenicity and hypersensitivity (Kirmanidou et al., 2016). As aforementioned, highly loaded applications on bone implantation might leads to fatigue failure. Ryan et al., (2006) reported that both Co-Cr alloys and Ti-6Al-4V alloys experienced drastic reductions in fatigue strengths when fabricated as porous coatings on solid core structures. They stated that stress intensification due to localized notch acted as stress concentration that affected implant strength in the region of the porous coating.

On the other hand, bacterial infection also distinguished in destruction of implant. This could accelerate the mechanical damage of spine implant and it is reported that bacterial adhesion is the first and most important step in implant infection (Ribeiro et al., 2012). Bacterial adhesion is a complex process and it is influenced by environmental factors, bacterial properties, material surface properties and by the presence of serum or tissue proteins. It is mainly related to the implant surface material properties. When bacterial adhesion occurs, surface colonization for certain bacterial species that capable of forming protective biofilm layer cannot be prevented. Therefore, it is essential to prevent implant-associated infection in order to inhibit bacterial adhesion. Moreover, this biofilm layer is extremely resistant to both immune system and antibiotics (Ribeiro et al., 2012).

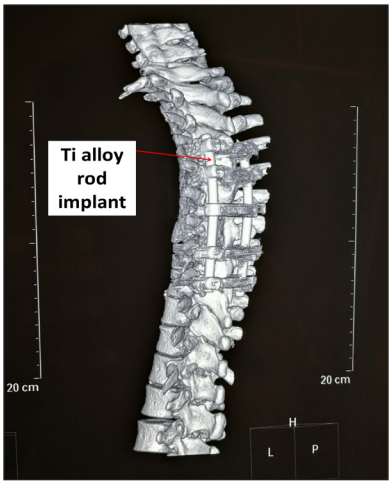

Figure 1. MRI image of spine implant taken from female patient's spinal cord having major surgical operation due to accident, (with 4.5 mm spinal locking plate and 5.5 mm Ti locking screws, Kuala Lumpur General Hospital, Malaysia)

SURGICAL SPINE IMPLANT CASE STUDY

A 44-year- old female involved in a motor vehicle collision presented with fractured spinal cord. Six years after her surgery, she developed increasing back pain with small wound. She returned with hardware infection and underwent extensive debridement of the infection site and removal of spine implant. Figure 1 shows an image of Ti-alloy spine implant taken from female patient's spinal cord before underwent major surgical operation of implant removal. Complete implant removal was suggested by the surgeon and it was considered essential to treat patient's infection. The patient is now over three months out from her final operation without any recurrences of infection and with great improvement in her pain.

Spinal infections from implants represent a difficult challenge in medical surgery. The situation when dealing with spine infection is more difficult and high risk challenge to the spinal surgeon and physician due to the requirement for stability and to protect neurological function (Quaile, 2012). Other than that, spinal infections can also be of acute onset and delayed appearance. As reported by Jung-Tung et al., (2015) postoperative surgical site infection (SSIs) is one of the most common complications after spinal surgery and the incidence of spinal SSIs in the literature is around 0.7 - 16.0%. From medical approach, these spinal infections often require extended antibiotic therapy, repeated surgery for wound debridement, hardware removal, and prolonged hospitalization (Crawford et al., 2015; Jung-Tung et al., 2015). Furthermore, as reported in previous literature, the spinal surgeries carry a higher risk of infection compared with other orthopaedic procedures.

In clinical and medical review, for an infection to occur at the surgical site, bacteria must be present at the operative or procedural site in substantial quantity which is $>10^5$ organism. As discussed by (Chaudhary et al., 2007), three possible sources of bacteria are direct inoculation at the time of surgery, soiling of the incision in the fresh postoperative phase, or through hematogenous seeding. They concluded that most post procedural infections were a consequence of direct inoculation. Instead of that, several patient-related factors play an important role in the pathogenesis of infection which includes modifiable and non-modifiable factors. Some non-modifiable factors are spinal trauma, diabetes, advanced age and development delay. Meanwhile, obesity, smoking, malnutrition and extended hospitalization are modifiable risk factors (Chaudhary et al., 2007; Quaile, 2012). Hoelzer et al. (2017) reported that retrospective review was conducted on 2737 unique implants or revisions of SCS (spinal cord simulation) systems. It showed that patient demographics, risk factors including diabetes, tobacco use, and obesity did not independently increase the rate of infection.

Basically, in this case study only failure analysis work was carried out. This methodology often regarded as a diagnostic post-mortem activity and in this work, it focused on Ti-alloy spine implant taken from female patient's spinal cord after underwent major surgical operation of implant removal. The outcomes of this observation can benefits

others as a learning process which sometimes are ignored or neglected. The failed of implants part had been initially observed only using visual observation technique and as for continuation, the experimental work on this parts will be carried out in our next article.

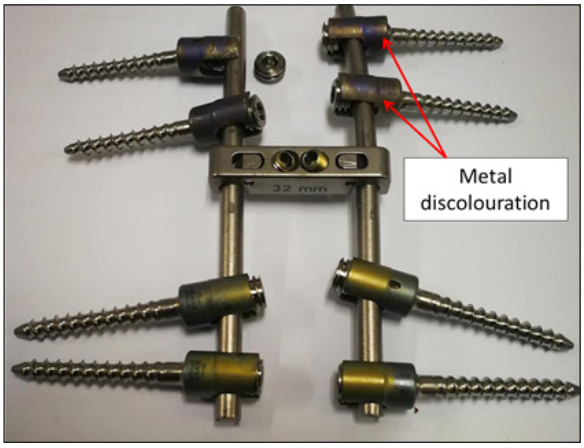

Figure 2. Photograph of the screws, rods and plate after implant removal

Apparently, it can be found that some location on the failed implants showed some colour changes as shown in Figures 1 and 2. The changes could be attributed by metal hypersensitivity. Metal hypersensitivity involves a metal exposure to degradation product such as wear particles of metal on metal bearing surfaces. It was found that it is in agreement with Sakellariou et al. (2011) that mostly the spinal implants are static load-bearing devices subjected to micro-motion. It is possible to indicate that the 6 years of implant usage might leads to spinal implant deformity which involve several couplings of screws, rods and interconnecting devices. It can be said that, all of the observation could be related to fretting corrosion.

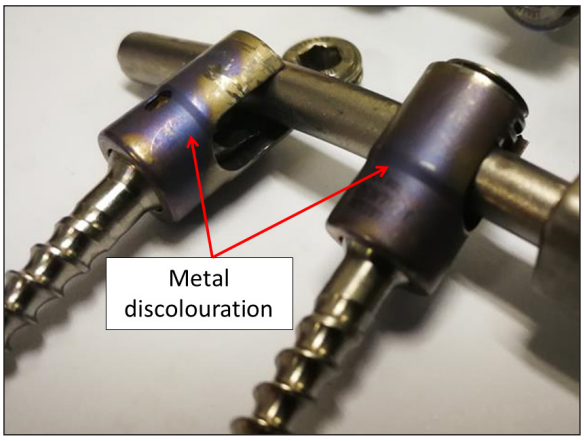

Figure 3. Enlargement and closed-up view in Figure 2 showing and effect of metal discoloration

In the presence of fretting, the condition may change because the passivating oxide layer may be abraded away, thus, expose the bare metal to the electrolyte solution (Jacobs et al., 1998). As shown in Figure 2, the Ti-alloy metal plate shows effects of discoloration which might related with the effects of corrosion degradation. As well discussed in previous study, metallic discoloration is uncommon disorder defined by the accumulation of metallic particles in the skin through the blood stream or surface application (Park et al., 2013).

In order to evaluate the relation of between corrosion and implant-related hypersensitivity reaction in patients, the presence of corrosion products can view significantly as shown in Figures 2 and 3. Several spots on Ti-implant location show some stain of metal discoloration related with corrosion effects and all of these can impair their function. As indicated, Ti or Ti alloy will initially discolour as it is oxidizes producing a colour changes on the surface of the metal. As reported by Takahashi et al. (2014) the discoloured location on Ti alloy surface was found to be thicker and it was presumed to be the result of the interference colour because of the thickness difference of the oxide film due to film growth. Moreover, corrosion which related with implant can result in a shortened instrument life which additionally could results in increased cost.

As well known, the surface of Ti and Ti alloys consist of a thin oxide layer which ranges from 2 to 6 nm. This protective oxide layer usually acts to protect the metal surface from further degradation. Moreover, this oxide layer is amorphous or poorly crystalline and is composed of a slightly oxygen-deficient titanium oxide (Takahashi et al., 2014). The oxide layer will be produced spontaneously to protect the metal surface. However, when the Ti is brought into contact with body fluid environment for long duration of exposure, a complex phenomenon will take place at the metal interface. Thus, the formation of oxide film is far thicker than the one obtained if it is exposed to simple immersion exposure. Furthermore, when the discoloured locations are subjected to simple motion for long periods of duration, this would lead to mechanical implant failure such as fretting corrosion.

In this case, it is possible to note that the metal discoloration on spinal instrumentation also can possibly cause metal ions release from fretting corrosion into patient's body fluids. Thus, causing back pain and the small wound that appeared at the surgical site as experienced by the 44-year old female patient as described earlier. As explained in Figure 4, the metal particles that are leached from the metal implant substrate as an output of fretting corrosion process under the influence of mild body tissue response. The releases of metal ions show effects of localized discoloration and metal hypersensitivity. These effects would lead to body inflammation, forming an infection from a small wound. These cause an increase in foreign body reaction leading to severe body tissue response and thus, loosening of the implant.

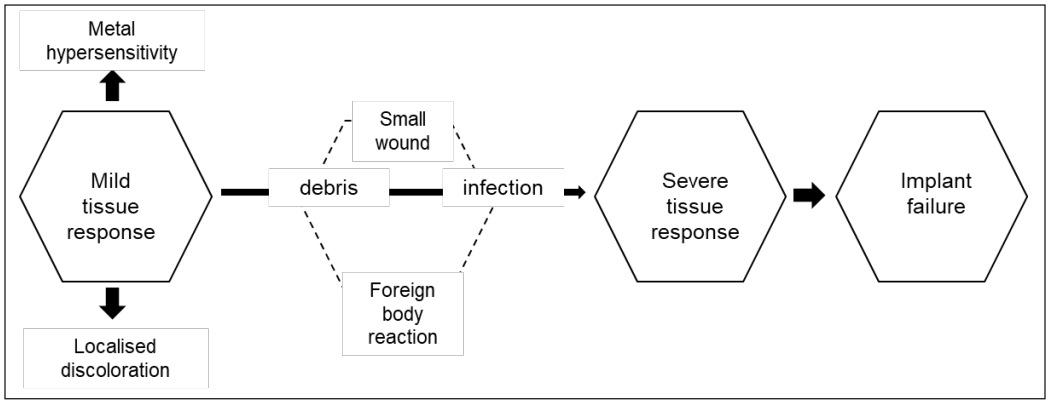

Figure 4. Body response to an implant failure

This finding is also in agreement with Singh et al. (2012), Simon and Fabry (1991), Niinomi and Nakai (2011) and Kirkpatrick et al. (2005). They reported that, instead of corrosion damage which involved spinal implants, mechanical failure such as fatigue was also observed in previous study. Singh et al., (2012) found that posterior spinal fusion implants subjected to micro-motion under physiological loading conditions inducing a potential for fretting corrosion which referred to the damage of contact surfaces. In Posterior Spinal Fusion (PSF) surgery, to stabilize the spine it involves an incision in the midline of the back (posterior) and in some patient metal screws and rods that are placed in the spine to hold the bones while the fusion heals. In this case when rubbing action between metal and tissue interface increase, the release of metal particulate wear debris shown to increase metal ion level which is dangerous to human body (Simon & Fabry, 1991). Niinomi and Nakai (2011) stated that, there was possibility of fretting fatigue condition especially in the contact area of two bodies such as between bone plate and screws. Kirkpatrick et al. (2005) also stated that Ti alloy implants showed no significant corrosion but had three constructs with fatigue failure of anchoring screws. They found to take preventive methods in minimizing the effects of localized changes over time especially on the implants surface finishes between rods and connectors which were the most susceptible to corrosion.

The other factor that might to take into consideration is the presence of bacteria inside the living human bodies which cause an infection to the implants. It is known as microbial induced corrosion (MIC). As investigated by Ayer et al., (2017) the nature of bacteria on the skin and deep dermal layers might lead to an infection which can occur when implanted metallic materials is utilized especially in spine and orthopedic procedures. Instead of that, the level of bacterial contamination also varies in relation to the grade of open fractures. It is also reported that even in clean surgical procedures, the low level of bacterial contamination must be assumed (Arens et al., 1996).

In this case, spine implant instrumentations can be affected also by corrosion. It may cause local and systemic complications. Although the diagnosis of corrosion is difficult several test were conducted by previous literature to detect the metal degradation. del Rio et al. (2007) conducted a study to determine and measure the metal levels on patients with posterior instrumented spinal fusion. They revealed that the patients with spinal implants without radiological signs of corrosion had increased levels of Cr in serum and urine compared to volunteers without implants. It can be said that, corrosion significantly raised the metal levels, including Ni and Cr in serum and urine when compared to patients without metallic implants. Beguiristain et al. (2006) reported that a after 14 years, a female patient with a 316L SS instrumentation presented progressive paraparesis during last 2 months. Plain radiography, computed tomography scan and computed tomography-scan-guided needle biopsy revealed that a metallotic mass penetrated into the spinal canal causing compression of the spinal cord implant at the T5-T6 level (Beguiristain et al., 2006). The results show that the patient's symptoms were related to the corrosion of the implant and it was found that the infection by Propionibacterium acnes. In this case, MIC is a concept to be taken into account and it is possible to conclude that the bacteria may modify the rate of metal corrosion (Beguiristain et al., 2006; Farnsworth et al., 2014).

It is well discussed in previous literature, pertaining to the corrosion of spine biomedical alloys which currently focused on galvanic, pitting, crevice and fretting corrosion. The real concern is on galvanic corrosion specifically when involved Ti-6Al-4V and CoCrMoC where these two alloys are in intimate contact. It is also observed in spine instrumentation where the mixing of these alloys is applied such as Ti-6Al-4V pedicle screw with CoCrMoC tulip and an interlocking Ti-6Al-4V or CoCrMoC spine rod (Ayer et al., 2017). It can be said that due to complex environment of human body, most likely for the corrosion of alloys in spine is fretting wear and microbial induced corrosion. It also depends on human body response and it is reasonable to note that living human body could provide nutrients for bacterial growth. As reviewed by Gitten et al., (2011) spine implant constructs consisting of pedicle screws, connectors, and rods that have mixed components made of stainless steel (SS) and Ti shows signs of galvanic corrosion under cyclic loads. The results showed an evidence of minor signs of corrosion at the interfaces between SS-Ti, Ti-Ti, and SS-SS. In this case, the surrounding tissue could serve as a medium for electrical flow between metallic implants (Gittens et al., 2011). Sakellariou et al. (2011) reported a case study on a 14 year-old girl with a history of extended posterior spinal fusion due to idiopathic scoliosis. They identified two potential contributing factors for the development of a secondary systematic reaction which were late infection which was not unusual and metal allergy to Ti or Ti-alloy components that was relatively rare to be found.

CONCLUSION

In this study, the importance of using Ti and Ti-based alloys in biomedical implantation, especially in orthopaedic spinal cord injury was successfully reviewed. From the case study, it is possible to propose that the possibility of metal particles that are leached from the metal implant substrate as an output of fretting corrosion process under the influence of mild body tissue response. The releases of metal ions show effects of localized discoloration and metal hypersensitivity on implant instrumentation. These caused body inflammation, forming an infection from a small wound of the human's body. Thus, increase in foreign body reaction leads to severe body tissue response and finally, loosening of the implant. Based on our comprehensive review of the literature and randomized studies with a focus on the failed part of implant usage, it shows that scientific evidence for in-depth analysis of the failed part are lacking especially in a real case study since the sampling method is limited. Further, well-designed studies are necessary to better understand the possible corrosion mechanism concern.

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