THE ISSUE OF CORROSION IN DENTAL IMPLANTS: A REVIEW

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ABSTRACT
Pure titanium or titanium alloys, and to a lesser extent, zirconium, are metals that are often used in direct contact with host tissues. These metallic biomaterials are highly reactive, and on exposure to fluid media or air, quickly develop a layer of titanium dioxide (TiO₂) or zirconium dioxide (ZrO₂). This layer of dioxide forms a boundary at the interface between the biological medium and the metal structure, determining the degree of biocompatibility and the biological response of the implant. Corrosion is the deterioration a metal undergoes as a result of the surrounding medium (electrochemical attack), which causes the release of ions into the microenvironment. No metal or alloy is entirely inert in vivo. Corrosion phenomena at the interface are particularly important in the evolution of both dental and orthopedic implants and one of the possible causes of implant failure after initial success. This paper comprises a review of literature and presents results of our laboratory experiments related to the study of corrosion, with special emphasis on dental implants. In situ degradation of a metallic implant is undesirable because it alters the structural integrity of the implant. The issue of corrosion is not limited to a local problem because the particles produced as a result could migrate to distant sites, whose evolution would require further studies.

Key words: corrosion, dental implants, macrophages, failures.

INTRODUCTION
The discovery of relatively inert metallic and alloy biomaterials has led to their use in the field of biomedical applications such as orthopedics and dentistry. They are being increasingly used due to their physical-chemical properties and compatibility with biological surroundings¹. Pure titanium or titanium alloys, and to a lesser extent, zirconium, are the metals that are most often used in direct contact with host tissues. These metal-

LA PROBLEMÁTICA DE LA CORROSION EN IMPLANTES ODONTOLOGICOS

RESUMEN
El titanio puro o en aleación, y en menor grado el circonio, son los metales más utilizados en contacto directo con los tejidos del huésped. Estos biomateriales metálicos son muy reactivos y al exponerse a medios líquidos o al aire, desarrollan rápidamente una capa de dióxido de titanio (TiO₂) ó de dióxido de circonio (ZrO₂). Esta capa de dióxido limita la interfase entre el medio biológico y la estructura metálica, determinando el grado de biocompatibilidad y la respuesta biológica del implante. La corrosión es el deterioro que sufre un metal debido al medio que lo rodea (ataque electroquímico) y que produce como consecuencia la liberación de iones en el microambiente. In vivo ningún metal o aleación es completamente inerte. Los fenómenos de corrosión, en la zona de la interfase, son de especial importancia en la evolución de los implantes tanto odontológicos como ortopédicos y constituyen una de las posibles causas de fracaso de un implante luego del éxito inicial. El presente trabajo comprende una revisión bibliográfica y la presentación de resultados de las experiencias de nuestro laboratorio relacionadas con el estudio de la corrosión, con especial énfasis en los implantes odontológicos. La degradación “in situ” de un implante metálico es un hecho no deseable ya que altera la integridad estructural del implante. La problemática de la corrosión no se limitaría a un problema local dado que las partículas resultantes de este proceso podrían migrar a sitios alejados del sitio del implante, cuya evolución plantea interrogantes para futuros estudios.

Palabras clave: corrosión, implantes odontológicos, macrófagos, fracasos.
Biomaterials are highly reactive and when exposed to fluid media or air, quickly develop a layer of titanium dioxide (TiO₂) or zirconium dioxide (ZrO₂). This layer of dioxide forms a boundary at the interface between the biological medium and the metal structure. It produces passivation of the metal, determining the degree of biocompatibility and the biological response of the implant. Titanium dioxide exists naturally mainly in the form of three crystalline structures: rutile, anatase and brookite. In titanium implants, the passivating oxide layer is made up of anatase and rutile or anatase alone.

The use of titanium dental implants has revolutionized oral implantology. In the USA, about 300,000 patients a year currently receive dental implants. With the aim of improving their biocompatibility and mechanical resistance, their manufacture attempts to achieve adequate design and minimum degradation, corrosion, dissolution, deformation and fracture. Corrosion is the deterioration of a metal as a result of the surrounding medium (electrochemical attack), which causes ions to be released into the microenvironment. There are “noble” metals such as rhodium (Rd), palladium (Pd), iridium (Ir) and platinum (Pt), which owe their resistance to corrosion to high thermodynamic stability. Metals known as passivable, such as titanium (Ti), vanadium (V), zirconium (Zr), niobium (Nb) and tantalum (Ta), are thermodynamically unstable and owe their resistance to corrosion to the formation of a protective surface layer of oxide.

No metal or alloy is entirely inert in vivo. Corrosion is one of the possible causes of implant failure after initial success. Therefore, management and control of corrosion is a crucial problem from both a biological and metallurgical en economic standpoint.

Corrosion should be analyzed with an interdisciplinary focus and the participation of chemists, biologists, physicists, engineers, metallurgists and biomedical specialists. The issue of corrosion has been researched by means of systematic histological studies at the Biomaterials Laboratory, which has a Failed Dental Implant Service. At the implant-tissue interface bone tissue (osseointegration), medullary tissue (myelointegration), fibrous tissue and/or inflammatory reactions can be found. At the lab, human dental implant failure is most often caused by mobility, metal fracture (fatigue) or early exposure.

It is worth noting that the interface of implants that have failed due to metal fatigue are found to have good osseointegration. In this case, the implant is successful from a biological standpoint (osseointegration) but a clinical failure from the mechanical standpoint. Guglielmotti and Cabrini found metal particles included in the osseointegrated bone tissue and the bone medulla of implants that failed due to metal fatigue, providing evidence of the corrosion of the metallic structure.

Olmedo et al. found macrophages loaded with metal particles as indicators of the corrosion process in the soft peri-implant tissue of failed human dental implants (Fig. 1 A-B). Microchemical analysis of the particles contained in the macrophages, determined by x-ray dispersion (EDX) analysis, confirmed the presence of titanium. It is worth noting that the number of loaded macrophages was greater in the proximity of metal surface of implants than at a distance from it.

In the field of oral and maxillofacial surgery, titanium is widely used as an implant in the form of membranes, grids, reduction plates, screws and distractors, among others. According to the literature, the removal of titanium miniplates once the bone has healed is usually considered unnecessary precisely because of titanium’s excellent biocompatibility and resistance to corrosion. This is beneficial for the patient, who need not undergo a second surgical procedure. Furthermore, some maintain that the mini-plates should only be removed if they cause complaints and in cases of wound dehiscence or infection. However, as mentioned above, no metal or alloy is entirely inert in vivo. In this regard, some authors claim that titanium miniplates should be removed, to allow for physiologic bony adaptation and avoidance of a foreign body reaction. Thus, whether or not titanium mini-plates or grids should be removed after the bone has healed is still a matter of controversy. We have conducted experimental assessment of the biological effect of a type of localized corrosion – pitting – in the peri-implant environment. From a histological standpoint, we found little osseointegration with extensive zones of soft tissue in the metal-tissue interface and the presence of corrosion products in the peri-implant environment, especially surrounding the blood vessels, to be drained by them (Fig. 2). Local adverse effects...
produced by this kind of corrosion and observed in this study suggest caution in the use of titanium plates and grids as permanent fixation structures. Corrosion phenomena at the interface are especially important in the evolution of both dental and orthopedic implants. The issue of corrosion may not be limited to a local problem because particles produced as a result of corrosion may migrate to sites far from the implant. This subject is of particular interest in studies of biocompatibility.

DISSEMINATION OF TITANIUM TO OTHER BIOLOGICAL COMPARTMENTS
The local effect of corrosion with the consequent passage of metal particles to the peri-implant biological medium may also compromise other biological compartments.

In the field of orthopedics there are data that state that titanium ions pass into the surrounding tissues, reach the inner medium and are excreted in urine\(^1\). Different researchers have found metal ions in body fluids and organs. Galante et al.\(^1\) studied osseointegrated coxofemoral prostheses made from titanium 90% - aluminum 6% - vanadium 4%, showing that ions of all three metals pass into the plasma and are excreted in urine. In autopsies, Urban et al. found metal and plastic particles from coxofemoral prostheses and knee replacements in organs such as liver, spleen and lymph nodes\(^1\).

As previously described, titanium and zirconium implants have a protective surface layer of dioxide (TiO\(_2\) or ZrO\(_2\)). This layer is responsible for biocompatibility and forms a boundary of the interface between the biological medium and the implant, reducing its reactivity and partially preventing corrosion\(^3,4,7\). With the aim of assessing the pathways of the dissemination of corrosion products and estimating the
how much is deposited in different biological compartments, we have developed experimental models using animals which are subject to intraperitoneal injection of TiO$_2$ or ZrO$_2^{19-24}$. During these experiments we made histological observations and quantified titanium and zirconium deposits in organs with macrophagic activity such as liver (Fig. 3), spleen and lung$^{19}$. For equivalent doses and times there was always more titanium deposited than zirconium. In addition, we found titanium or zirconium particles in monocytes (Fig. 4) and blood plasma$^{22,24}$. The detection of titanium or zirconium in the blood (cells and/or plasma) of patients with prostheses (coxofemoral, dental, plates and screws for fracture reduction, metal plates for reconstruction of large zones) could be used as an indicator of the presence of a corrosion process of the metal structures. It is known that traces of metal can increase the physiological production of reactive oxygen species (ROS), which, without a compensatory increase in antioxidant species, leads to tissue damage$^{25-27}$. We have proved the presence of titanium and zirconium particles in lung phagocytes identified immunohistochemically as CD68 macrophages$^{28}$. The evaluation of the oxidative metabolism of lung macrophages exposed to these oxides shows an increase in ROS generation. Nevertheless, it should be noted that ROS levels in animals exposed to ZrO$_2$ are markedly lower than the levels found in animals exposed to TiO$_2$. The data suggest that zirconium is more biocompatible than titanium$^{23,24}$.

**CLINICAL IMPLICATIONS OF CORROSION**

It is concluded from the analysis of failed human dental implants and the information obtained from experimental models that any titanium surface might undergo a process of corrosion with particles passing into the local biological and systemic medium. Biochemical changes in the peri-implant microenvironment can lead to corrosion of the implant. In traumatized tissues significant drops in pH values have been found, reaching values as low as pH 4 during the healing process$^{29}$. These values greatly increase the aggressiveness of tissues towards metallic materials. We have found that the reduction of pH in the electrolytic medium as a consequence of local inflammatory processes may also act as a corrosion-stimulating agent$^{30}$. The corrosion process may limit the metal’s resistance to fatigue, compromising its resistance, which may eventually cause the fracture of the implant$^{31-34}$. It has been reported that saliva leaking between the suprastructure (nickel-chrome-molybdenum alloy) and the implant (made of pure titanium) may trigger a corrosion process (galvanic corrosion) due to differences in electrical potential. This generates the passage of ions such as nickel or chrome from the alloy of a crown or bridge to the peri-implant tissues, with consequent bone reabsorption and may compromise the mobility of the implant and its subsequent fracture$^{31}$. The release of ions/particles may produce pigmentation of the soft tissues adjacent to an implant (metallosis)$^{35}$. In one experiment we made a histological assessment of tissue response in human oral mucosae associated to submerged titanium implants, using biopsies of human oral mucosae from the area covering the implant’s closure screw. That study identified particles of different sizes, either free or taken up by macrophages, in the connective tissue (Fig. 5). In addition, scanning electron microscope
images showed depressions and irregularities on the surface of metal caps. It would be interesting to relate possible biological action of these particles with the evolution of the implant\textsuperscript{36}.

The products of corrosion of the metal implant may behave as haptenes, generating a hypersensitivity reaction with release of inflammatory mediators known as cytokines and macrophage recruitment\textsuperscript{37-39}. It has not yet been proved whether hypersensitivity to metal is the cause of implant failure or vice versa\textsuperscript{37}. Similarly controversial is the issue of whether an inflammatory process is responsible for corrosion, or corrosion triggers an inflammatory process.

Furthermore, metal corrosion can affect the close contact between the implant and the bone tissue. Metal particles from coxofemoral prostheses can be ingested by macrophages, stimulating the release of cytokines that contribute to bone reabsorption by activating osteoclasts. In addition to increasing bone reabsorption, these particles can suppress the osteoblast function, reducing bone formation and contributing to osteolysis\textsuperscript{40,41}.

Titanium toxicology is a subject currently under discussion. According to epidemiological studies, inhalation of environmental dust containing titanium does not have a deleterious effect on lungs\textsuperscript{42,43} but other studies have suggested the association of titanium particles with pleural pathologies\textsuperscript{44}, granulomatous diseases and malignant lung neoplasm\textsuperscript{45}. The accumulation of metal particles in the liver might compromise its function, as described by Urban et al. in a study where the presence of titanium particles in a patient was associated to granulomatous reactions and hepatomegaly\textsuperscript{18}.

In experimental models, we have observed the presence of a considerable amount of titanium particles not only in macrophages but also in hepatocytes\textsuperscript{28}.

It has been reported that some of the metals currently used most often in the manufacture of implants, particularly in the field of orthopedics (titanium, aluminum, vanadium, cobalt, chrome, nickel) are potentially toxic\textsuperscript{46-51}. Their carcinogenic potential has been assessed in experimental studies on animals\textsuperscript{52-54}. Nevertheless, there are few reports on the possible development of malignant tumors associated to prosthetic structures in humans\textsuperscript{2,55,56}. In this regard, our work group has reported one case of sarcomatous degeneration in the proximity of a stainless steel metal prosthesis, with the aim of contributing with the pool of information to help define more certainly the potential toxicity and risks associated to the use of metallic implants\textsuperscript{57}. It is interesting to note that the International Agency for Research on Cancer (IARC) has recently classified TiO\textsubscript{2} as a possible human carcinogen\textsuperscript{58}.

“In situ” degradation of a metallic implant is undesirable because it alters the structural integrity of the implant. Implant manufacturing prospects aim at developing methods that will help reduce the passage of ions/particles from implants to tissues, in order to minimize the adverse effects of corrosion. We believe that further studies are needed, in particular long-term studies, to continue defining the factors involved in implant corrosion and to establish the basic conditions for their use in clinical implantology.

It is important to stress that the adverse effects of corrosion described in this paper do not always occur in patients with implants, because the biological response varies among individuals.

**ACKNOWLEDGEMENTS**

This study was supported by the grants: BID 1728/OC-AR - PICT 33493 from the National Agency for the Promotion of Science and Technology, O-020 from University of Buenos Aires, CONICET PIP6042 and Roemmers Foundation, Argentina.

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