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BIOCOMPATIBILITY AND BIOTOLERABILITY OF TITANIUM-BASED MATERIAL USED IN MEDICINE

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S u m a r y. Titanium is an extremely durable and chemically resistant metal. Due to its properties it is widely used in industry. Medical applications of Ti and Ti alloys are mainly focused on the use of rods, implants, plates, cages, valves and pins, even needles and stents. Those devices support the treatment of spinal curvature, reconstruction of bone tissue and ligaments or they shield the internal organs if natural protection is missing. The extensive use of titanium is related, among others, to its high biocompatibility.
The paper briefly discusses the characteristics of titanium and its alloys used in medicine.

K e y w o r d s: titanium, biomaterials

INTRODUCTION

Metallic biomaterials have a great significance in medicine. They are used to temporarily or permanently replace the parts of tissue or organ and take over their function. Since biomaterials have contact with human body, they should meet strict criteria such as high tolerance to corrosion, good mechanical and abrasion resistance, uniformity, lack of toxicity, biocompatibility, low thrombogenicity, and the cost of their production should be relatively low. They are used, among others, to produce surgical devices applied in medicine and dentistry, e.g. intramedullary needles, surgical bone plates, screws and bone wires, needles, and stents and prosthetic devices.

The most common metallic biomaterials include cobalt, titanium shape-memory alloys, and austenitic steels composed of chromium (16-25%), nickel (above 8%), molybdenum (ok 3 %), manganese and nitrogen.

The review focuses on titanium and Ti-based alloys, their physicochemical properties, biocompatibility and toxicity.

Physical and chemical properties of titanium

Metallic titanium has a great tensile strength (220 MPa) and hardness, density of 4.50 $g \cdot cm^{-3}$, melting point 1650-1670 °C and boiling point 3287 °C. Titanium is passive to a large number of chemical agents such as concentrated nitric and sulphuric acids, and solutions of most salts. This element exposed to above mentioned agents forms a thin layer of oxide on the surface, which additionally decreases its reactivity.

Naturally titanium occurs as minerals, such as ilmenite - $FeTiO_3$ and rutile - TiO_2 , and it takes ninth position on the list of elements occurring in Earth's crust. Titanium contents in human body are quite low, ca. 0.3 $mg \cdot L^{-1}$ in the serum, and in the lungs - 3.7 $mg \cdot kg^{-1}$ wet weight, kidney cortex - 1.3 mg·kg^{-1} wet weight, liver - 1.3 mg·kg^{-1} wet weight, brain - 0.8 mg·kg^{-1} wet weight, and the muscles - 0.2 mg·kg^{-1} wet weight [6, 7].

Titanium occurs in two allotropic forms: alpha and beta, which have different properties. Alpha form has a lower durability but is more formable than beta form (Table 1). Furthermore, titanium combined with other metals (stabilizers) forms alloys, and their physical properties are different than pure metal. High tensile strength and hardness, high melting and boiling point in combination with a relatively low density and excellent corrosion resistance makes titanium and its alloys a suitable material for industrial applications. It is used in aerospace industry for the production of airplane parts such as gas turbine engines, engine cowlings and heat shields. Ti-based materials are also applied in medicine and dentistry as a main component of hip and knee joint prostheses, bone screws and plates, dental implants, surgical devices and heart valves.

Biocompatibility of titanium

In 2011 Buddy D. Ratner proposed a new definition of biocompatibility. According to the definition: "biocompatibility is the ability of a material to locally trigger and guide non-fibrotic wound healing, reconstruction and tissue integration" [8]. For materials widely used in medicine, he offered the term of 'biotolerability' as the ability of a material to reside in the body for long periods of time with only low degrees of inflammatory reaction [8].

Despite great chemical resistance of titanium, none of its alloys stay inert *in vivo* conditions. Koike and Fujii tested the resistance to corrosion of pure Ti at various pH range of lactic and formic acids for 3 weeks at 37 °C. The investigation showed that corrosion resistance significantly depended on pH and had a tendency to increase at higher values. Furthermore, the thickness of TiO_2 passive layer also varied in tested solutions [2]. In 2011, Berglund and Carlmark found correlation between yellow nail syndrome and titanium and gold in patients with skeletal titanium implants and gold in their teeth. Titanium levels varied between 1.1 and 170 µg·g^{-1}, with a median level of 5 µg·g^{-1} in the finger nails of patients with implants compared to controls [1]. Another study by Martini *et al.* has also shown that Ti particles can be released into the bone tissues from implant and can migrate into newly formed bone [4].

Toxicity of titanium

Tamura *et al.* investigated the correlation between particles of metallic 99.9% pure titanium released from Ti alloys and inflammatory reaction, both *in vivo* experiment in Wistar rats and *in vitro* tests with human neutrophils [10]. Different size Ti particles were placed in the subcutaneous connective tissue in the abdominal region of rats, and after seven days from the implantation tissues were extracted and investigated. Intensive phagocytosis and the release of TNF-α, IL-1β and superoxide were observed near the agglomerated 2 µm metallic fragments. Both tests proved that particles bigger (10, 45 and 150 µm) than neutrophils could not be phagocyted, thus there was no inflammatory response. Furthermore, scanning by electron microscopy showed the deformations of some neutrophils in the solution containing 2 µm parts of Ti. Tamura *et al.* confirmed using inductively coupled plasma atomic emission spectroscopy that such effect was due to metallic titanium rather than its ions [10]. mRNA levels and increased expression of particular chemokines were observed after the exposure of monocytes to Ti alloy particles in a dose-dependent and time-dependent manner [5].

Lalor *et al.* also found large amounts of Ti particles in patients after re-operation of failed total hip replacements. Moreover, a lot of T-lymphocytes and almost no B-lymphocytes were found using monoclonal antibody markers, which suggests type IV hypersensitivity, cell-mediated and delayed response [3]. Another research performed by Rogers *et al*. showed that human monocytes exposed to different Ti alloy particles at concertation $4 \cdot 10^7$ particles·ml^{-1} produced prostaglandin E_2. Apart from the production of prostaglandin E_2, the release of cell mediators, tumour necrosis factor, Il-1 and Il-6 were also observed. Despite above mentioned reactions, none of the studies proved significant toxicity of Ti particles, and 98% cell viability was maintained, which is equal to non-stimulated cells [9]. According to new definition of biocompatibility and biotolerability given by Buddy D. Ratner, it can be stated that titanium and its alloys have quite good biocompatibility, and ensure a good support of bone tissue regeneration; however, they are not fully biotolerable as they are likely to induce inflammation.

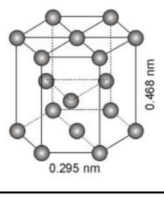
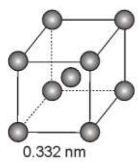
CONCLUSIONS

The review suggests that titanium remains completely inert *in vivo* conditions. Its corrosion resistance depends on pH value and presence of other substances in the medium. Human cells exposed to Ti particles produce agents leading to the inflammatory response such as release of Il-1 and Il-6, tumour necrosis factor, prostaglandin E2. Despite its drawbacks described in the literature, Ti and Ti-based materials are still commonly used for medicinal purposes due to titanium physical and chemical properties.

REFERENCES

1. Berglund F., Carlmark B., 2011. Titanium, sinusitis, and the yellow nail syndrome. *Biological Trace Element Res.* 143(1), p.1–7.
2. Koike M., Fujii H., 2001. The corrosion resistance of pure titanium in organic acids. *Biomaterials* 22(21), p.2931-2936.
3. Lalor P.A., Revell P.A., Gray A.B., Wright S., Railton G.T., Freeman M.A., 1991. Sensitivity to titanium a cause of implant failure? J *Bone Joint Surg*. British volume 73(1), p.25-28.
4. Martini D., Fini M., Franchi M., Pasquale V.D., Bacchelli B., Gamberini M., Tinti A., Taddei P., Giavaresi G., Ottani V., Raspanti M., Guizzardi S., Ruggeri A., 2003. Detachment of titanium and fluorohydroxyapatite particles in unloaded endosseous implants. *Biomaterials*. 24(7), p.1309-1316.
5. Nakashima Y., Sun D.H., Trindade M.C., Maloney W.J., Goodman S.B., Schurman D.J., Smith R.L., 1999. Signaling pathways for tumor necrosis factor-alpha and interleukin-6 expression in human macrophages exposed to titanium-alloy particulate debris in vitro. *J Bone Joint Surg. American* Volume 81(5), p.603-615.
6. Nordberg G., Fowler B. A., Nordberg M., 2007. Handbook on the toxicology of metals, Academic Press San Diego.
7. Nuevo-Ordóñez J., Montes-Bayón M., Blanco-González E., Paz-Aparicio J., Diánez Raimundez J., Tejerina J.M., Peña M. A., Sanz-Medel A., 2011. Titanium release in serum of patients with different bone fixation implants and its interaction with serum biomolecules at physiological levels. *Analyt Bioanalyt Chem* 401, p.2747–2754.
8. Ratner B.D., 2011. The biocompatibility manifesto: Biocompatibility for the twenty-first century. *J Cardiovasc Translat Res* 4(5), p.523–527.
9. Rogers S.D., Howie D.W., Graves S.E., Pearcy M.J., Haynes D.R., 1997. In vitro human monocyte response to wear particles of titanium alloy containing vanadium or niobium. The *J BoneJoint Surg. British vol* 79(2), p.311-315.
10. Tamura K., Takashi N., Kumazawa R., Watari F., Totsuka, Y., 2002. Effects of particle size on cell function and morphology in titanium and nickel. *Materials Transactions* 43(12), p.3052-3057.

Table 1. Forms of titanium and their properties.

Titanium form	alpha	beta
Vickers hardness test	230 HV	280 HV
Young's modulus	100 GPa	80 GPa
Crystal system		
Stabilizers	Al, Ga, Ge, C, O, N	Mo, V, Ta, Nb, Mn, Fe, Cr, Ni
Stability	to 882 °C	882 °C - 1668 °C