Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 13 (62) No. 1 – 2020
https://doi.org/10.31926/but.ms.2020.62.13.1.6

MAY DENTAL MATERIALS HAVE POTENTIAL SYSTEMIC SIDE-EFFECTS?

G. SCOIPAN[1*] A.M. BOȚIANU[2] L. NEDELCU[1]

Abstract: *In recent years, with the developments in biomaterial engineering, there has been an important progress in the field of dentistry. Dental implant is routinely used as the best treatment for teeth replacements. However, caution should be used in its application, because of its role in the development of inflammation, and its effect on the immune system and therefore, possible side effects following treatment. An implant is accepted and fulfills its role depending on a number of factors that govern the overall reaction of the body, of which the material from which it is made is essential. The main purpose of this article is to briefly present literature data on the systemic side effects of the various dental materials used.*

Key words: *dental implant, biomaterial, biocompatibility, side-effects*

1. Introduction

Each tooth from the structure of the stomatognathic system represents an essential biological complex, both in the case of animals, and especially in the case of humans. The most common organ failure encountered in daily clinical practice is tooth loss, as a result of dental caries frequently, or periodontal disease. Also, traumatic, congenital or chronic diseases may trigger loss of teeth.

Regardless of the age at which it occurs, tooth loss is a traumatic experience with unpleasant consequences, physical and mental, over time, especially if they are not replaced. Besides the local consequences, of aesthetic nature and functional (mastication and phonation), there may be also consequences for entire quality of life [14], [26].

[1] Department of Fundamental, Prophylactic and Clinic Disciplines, Faculty of Medicine, *Transilvania* University Brasov
[*] Corresponding author: geanina.timofte@unitbv.ro
[2] Department of Medical and Surgical Specialties, Faculty of Medicine, *Transilvania* University Brasov

Comparing to the beginning of Branemark introduction of oral implants in 1960s, when they became a treatment option for edentulousness patients, in the last years implantology has seen a spectacular development due to the dynamics of biomaterial engineering, the evolution of surgical or prosthetic techniques and methods [3].

Before to be used in dentistry, in order to protect the patient health, all materials should be periodical evaluated for biocompatibility using available screening assays. Biocompatibility can be defined as the property of a restorative material to be accepted by the body without generating local or systemic side effects.

Therefore, a biomaterial should be non-toxic, without inflammatory reactions when it is used as an implant [5], [25].

In this respect, it should be harmless to the oral or dental tissue, hemocompatible, without allergic or carcinogenic, side-effects. Moreover, must be corrosion-resistant, and easily adaptable to clinical and laboratory technologies [17].

Based on biocompatibility, dental used biomaterials can be classified as bio tolerant, bio inert and bioactive [18].

The most used biomaterials for dental implants are bioinert ones, including titanium and titanium alloys, as well as bioactive ones, including ceramics, calcium phosphate and hydroxyapatite. Aluminum oxides and other alloys are sometimes used, dental amalgam also [4].

2. Dental Materials

Upon contact with biological environments, including the oral cavity, any biomaterial finds particular physiological conditions with which it interacts through specific processes, but also through less predictable physiological mechanisms (local and systematic). Therefore, maintaining it for a long time may cause unwanted reactions [24].

Some authors consider that the physico-chemical properties of biomaterials, together with their biocompatibility are representative for their successful use in clinical practice. However, there are well-known cases of local or systemic side-effects induced by dental materials [18].

Most reported adverse reactions related to the composition of the biomaterial are to dental amalgam. The incidence of local side effects, such as oral lichenoid reactions, secondary to amalgam restorations is much more common compared to side effects other biomaterials. However, in rare cases, major adverse reactions have been reported [23].

According to the World Health Organization, the main source of inorganic mercury and mercury vapors is dental amalgam [6], [10]. Due to corrosion, each metal dental restoration can release cations. Based on numerous in vitro studies, this ion diffusion is found both in the oral cavity and in the systemic circulation, and may be the etiological agent of some local and systemic side-effects [2], [5].

There are authors who state that in the etiopathogenesis of some autoimmune diseases or allergic diseases an important role is played by metal-induced inflammation, being present symptoms such as: chronic fatigue, cognitive impairment, or joint and muscle pain. In this regard, Stejskal et al. postulated that in vivo, metal ions released from implanted materials can cause T-cells activation, generating systemic inflammation, which in turn, may affect

the brain and the hypothalamus - pituitary - adrenal axis, and also may trigger inflammation in susceptible subjects [21], [22].

On the other hand, Kisakol [8] and Guzzi et al. [7] in their studies did not observe any significant relation between amalgam and autoimmune thyroiditis or renal autoimmunity. Moreover, the pathogenic role of amalgam restorations could not be highlighted in a meta-analysis on multiple sclerosis [1].

Certain elements from titanium alloys, such as beryllium, chromium, cobalt, can cause allergic side effects [23]. The appearance of an autoimmune disease can be influenced, according to Rachmawati et al., by oral exposure to nickel.

But, there has been no study published on the potential mutagenic or teratogenic effects of metallic dental materials [15].

To sum up, the data in the literature regarding the potential local and systemic side effects of dental alloys, or secondary to ion release, are contradictory. It is therefore necessary to establish more clearly how the cations are released in the oral environment, their interaction with the tissues, as well as the response of the host [5].

2.1. Dental implants

Cases of hypersensitivity to titanium dental materials have been reported in the form of dermatitis, the appearance of non-keratinized hyperplastic gingivitis or in the form of rashes.

Osman et al. support the hypothesis that titanium can produce hypersensitivity reactions in susceptible patients and can be incriminated in triggering implant failure [13].

Titanium allergy was also noticed in a prospective study performed on a group of 1.500 patients who had a dental implant for at least 3 years [19].

Although titanium and zirconium are recognized in the literature as bioinert dental materials, some studies have highlighted the toxic hematological and metabolic potential of these materials, considering that these side effects are underestimated and underdiagnosed. More precisely, the etiological factor of an implant failure can be omitted by not knowing the toxic and allergic potential of these dental materials [18].

Also, Siddiqi et al. suggests that rare or non-specific clinical presentations, as well as their lack of recognition, may be the cause of under-reporting the incidence of allergic reactions to titanium dental materials as a potential etiological factor in implant failure [20].

In a study of 56 patients with titanium-based dental or endoprosthetic implants, Müller and Thon assessed a link between the presence of titanium exposure and the occurrence of adverse reactions in patients with chronic exposure. Thus, they observed that all patients included in the study developed, after exposure to titanium, nonspecific symptoms, such as joint or muscle pain, neuralgia, chronic fatigue syndrome, neurological disorders, or psychiatric disorders [12].

Improper implant integration as well as changes in chronic inflammation can lead, in some cases, to negative consequences, from peri-implantitis to implant failure [9].

Schedle et al. considers that intraoral lesions can be linked to dental restorations as a cause-and-effect mechanism by applying questionnaires to patients. Instead, for extraoral lesions it is

more difficult to establish causality and a link with the dental materials used.

In this sense, they proposed a more complex evaluation, starting from the patient's history, the signs and symptoms present, to the identification of the etiological agent when possible. Moreover, it suggests the need to establish a causal relationship. Thus, it opines for the demonstration of the disappearance of the symptoms after the removal of the triggering factor, as well as their reappearance in case of a new exposure. However, some of the requirements may conflict with ethical principles [17].

3. Biomarkers for Systemic Inflammation and Tests for Hypersensitivity Reactions

Patch test can be used in vivo to identify allergic reactions to metals [16]. In vitro, lymphocyte transformation test - LTT measures the degree of proliferation of lymphocytes from the peripheral blood in the presence of a potential allergen after an incubation period. The recorded results are reported as a stimulation index.

A first step towards therapeutic success is identification of patients with allergic susceptibility to metals, in order to remove incompatible restorative dental materials. In this regard, there are several case reports and clinical trials in which it has been observed that the replacement of the dental metal alloy or amalgam causes a significant clinical improvement in allergic patients [21].

Some authors claim that implanted materials can induce a mixed pro / anti-inflammatory phenotype, which sustains the development of chronic inflammation and along with microbial contamination may cause implant failure [9].

In order to identify predictive biomarkers for systemic inflammation according to dental implants, Merino et al. evaluated the long-term impact of dental titanium materials on the L-Kynurenine/L-Tryptophan ratio. Also, they investigated whether there are changes in systemic inflammatory mediators (cytokines and soluble fractalin (CX3CL1) and chemoattractant proteins monocyte-1 (MCP-1) chemokines) in these patients compared to the control group. They observed a higher systemic level of the L-kynurenine/L-tryptophan ratio in the group with long-term titanium dental implants or dental amalgam, which could indirectly predict osseointegration [11].

4. Conclusion

As can be seen, side-effects to dental materials used in clinical practice may occur, but their incidence and prevalence are difficult to assess.

In addition, there is little evidence data available in the literature. Over and above, the current article has limitations related to the fact that only articles in English were researched, without covering the non-English literature.

It is therefore necessary to perform further in vitro studies, along with clinical trials. Equally important are screening tests to detect any potential toxicity of a dental material before its application in practice.

References

1. Aminzadeh, K.K., Etminan, M.: *Dental amalgam and multiple sclerosis: a systematic review and meta-analysis*. In: J. Public Health Dent., 2007, 67, p. 64–66.

2. Anusavice, K., Shen, C., Rawls, R.: *Biocompatibility*. In: Phillips' Science of Dental Materials, 2012, p. 142-143.
3. Brånemark, P., Hansson, B., Adell, R., et. al.: *Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period*. In: Scand. J. Plast. Reconstr. Surg., 1977, 16, p. 1–132.
4. Brooks, B.J., Brooks, A.E., Grainger, D.W.: *Antimicrobial Medical Devices in Preclinical Development and Clinical Use*. In: *Biomaterials Associated Infection: Immunological Aspects and Antimicrobial Strategies*, Zaat, S.A.J., Busscher, H.J., Moriarty F.T. (eds.). Springer Science&Business Media, p. 324-325.
5. Elshahawy, W., Watanabe, I.: *Biocompatibility of dental alloys used in dental fixed prosthodontics*. In: Tanta Dental Journal, 2014, 11(2), p. 150-159.
6. Guzzi, G., Grandi, M.: *Dental amalgam and mercury levels in autopsy tissues: food for thought*. In: Am J Forensic Med Pathol., 2006, 27, p. 42–5.
7. Guzzi, G., Fogazzi, G.B., Cantù, M., et al.: *Dental amalgam, mercury toxicity, and renal autoimmunity*. In: J Environ Pathol Toxicol Oncol., 2008, 27(2), p. 147-155.
8. Kisakol, G.: *Dental amalgam implantation and thyroid autoimmunity*. In: Bratisl Lek Listy., 2014, 115(1), p. 22-24.
9. Kzhyshkowska, J., Gudima, A., Riabov, V., et al.: *Macrophage responses to implants: prospects for personalized medicine*. In: J Leukoc Biol., 2015; 98(6):953-962. DOI: 10.1189/ jlb.5VMR0415-166R
10. Lorscheider, F.L., Vimy, M., Summers, A.O.: *Mercury exposure from "silver" tooth fillings: emerging evidence questions a traditional dental paradigm*. In: FASEB J., 1995, 9, p. 504–8.
11. Merino, J.J., Cabaña-Muñoz, M.E., Toledano G.A., et al.: *Elevated Systemic L-Kynurenine/L-Tryptophan Ratio and Increased IL-1 Beta and Chemokine (CX3CL1, MCP-1) Proinflammatory Mediators in Patients with Long-Term Titanium Dental Implants*. In: J Clin Med., 2019, 8(9), p.1368.
12. Muller, K.E., Valentine-Thon, E.: *Hypersensitivity to titanium: Clinical and laboratory evidence*. In: Neuro Endocrinol Lett, 2006, 27 (Suppl 1), p. 31-35.
13. Osman, R.B., Swain, M.V.: *A Critical Review of Dental Implant Materials with an Emphasis on Titanium versus Zirconia*. In: Materials (Basel*).*, 2015, 8(3), p. 932-958.
14. Pihlstrom, B.L., Michalowicz, B.S., Johnson, N.W.: *Periodontal diseases*. In: *Lancet*, 2005, 366(9499), p. 1809-20.
15. Rachmawati, D., Muris, J., Scheper, R.J., et al.: *Continuing the quest for autoimmunity due to oral metal exposure*. In: Autoimmunity, 2015, 48(7), p. 494-501.
16. Schalock, P.C., Menné, T., Johansen, J.D., et al.: *Hypersensitivity reactions to metallic implants - diagnostic algorithm and suggested patch test series for clinical use*. In: Contact Dermatitis, 2012; 66(1):4-19.
17. Schedle, A, Ortengren, U., Eidler, N., et al.: *Do adverse effects of dental materials exist? What are the consequences, and how can they be diagnosed and treated?* In: Clin. Oral

Impl., 2007, Res. 18 (Suppl. 3), p. 232–256.
18. Shahriar, S., Özcan, M., Solmaz, M.D.S., et al.: *A review on potential toxicity of dental material and screening their biocompatibility*. In: Toxicol Mech *Methods*, 2019, 29(5), p. 368-377.
19. Sicilia, A., Cuesta, S., Coma, G., et al.: *Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients*. In: Clin. Oral Impl. Res., 2008, p. 823-835.
20. Siddiqi, A., Payne, A.G.T., et al.: *Titanium allergy: Could it affect dental implant integration?* In: Clin. Oral Implants Res., 2011, 22, p. 673–680.
21. Stejskal, V., Hudecek, R., Stejskal, J., et al.: *Diagnosis and treatment of metal-induced side-effects*. *[published correction appears* In: Neuro Endocrinol Lett. 2007 Oct;28(5):iii], Neuro Endocrinol Lett., 27 Suppl 1, p. 7-16.
22. Stejskal, V.: *Metals as a common trigger of inflammation resulting in non-specific symptoms: diagnosis and treatment*. In: Isr Med Assoc J., 2014, 16(12), p. 753-758.
23. Syed, M., Chopra, R., Sachdev, V.: *Allergic Reactions to Dental Materials - A Systematic Review*. In: J Clin Diagn Res., 2015, 9(10), ZE04-ZE9.
24. Wataha, J.C., Messer, R.L.: *Casting alloys*. In: *Dent Clin North Am.*, 2004, 48(2):VII-VIII, p. 499-512.
25. Williams, D.: *On the mechanisms of biocompatibility*. In: Biomaterials., 2008; (20), p. 2941-53.
26. Yuan, Z., Nie, H., Wang, S., et al.: *Biomaterial selection for tooth regeneration*. In: Tissue Eng Part B Rev., 2011, 17(5), p. 373-388.