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# *Implant and Immunity in Neurosurgery*

## *Nöroşirurjide İmplant ve İmmünite*

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**Abstract:** Biological implants are widely used in neurosurgical operations especially in spine surgery. Many non-allergen metal implants have been developed such as titanium. Allergies agains other metal implants such as nickel, cobalt, and chrome, are common in the general population. Allergic reactions could cause complications such as intense pain, excessive inflammation, or rejection of implanted material/tissue. Implant life period depends on tissue implant reactions. Natural immunity and adaptive immune responses play a part in inflamatory reactions. Diagnostic tests could be done for metal implants allegy. In conclusion, if the titanium hypersensitivity reaction is proven, the definitive treatment is the removal of the device.
**Keywords:** Allergy, implant, immunity, neurosurgery

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**Özet:** Biyolojik implantlar, nöroşirürji operasyonları, özellikle omurga cerrahisinde yaygın olarak kullanılır. Titanyum gibi alerjik olmayan birçok metal implant geliştirilmiştir. Nikel, kobalt ve krom gibi diğer metal implantlara karşı alerjiler, genel popülasyonda yaygındır. Alerjik reaksiyonlar, şiddetli ağrı, aşırı iltihaplanma veya implant materyalin dokunun reddi gibi komplikasyonlara neden olabilir. İmplant ömrü, doku implantı reaksiyonlarına bağlıdır. Doğal bağışıklık ve adaptif bağışıklık tepkileri, enflamatuar reaksiyonlarda rol oynar. Metal implantları için tanı amaçlı testler yapılabilir. Sonuç olarak, eğer titanyum aşırı duyarlılık reaksiyonu kanıtlanmışsa kesin tedavi cihazın çıkarılmasıdır.
**Anahtar Kelimeler**: Alerji, implant, immünite, nöroşirurji

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## 1. Introduction

Titanium has started to be used as non-allergen metal in biological implants, especially in metal-sensitive individuals. However, titanium hypersensitivity is also seen rarely in some patients (1).

Allergies against metal, such as nickel, cobalt, and chrome, are common in the general population. It is estimated that 17% of women and 3% of men have a nickel allergy, and about 1 to 2% are allergic to cobalt, chrome, or both (2). Delayed-type hypersensitivity (DTH) is assumed to be responsible for such allergies.

Immunological reactions to implants occur in some patients. These allergic reactions could cause complications such as intense pain, excessive inflammation, or rejection of implanted material/tissue. As a result of immune reactions to implants, the patient's quality of life is decreased, the number of operations increases, the hospitalization period is extended, and the economic burden increases (3).

The foreign body reaction to the implants causes the formation of fibrotic capsules around the implant. As a result of the protein denaturation on the implant surfaces, an inflammatory immune response is induced. Mast cells, monocytes, and macrophages, which constitute the natural immune system, play a role in this reaction (4-6). Neutrophils are the first cells to respond to pathogens or sterile inflammation, which occur as a result of implantation of biomaterials. The main functions of neutrophils are to cause degranulation, the release of chemokines and cytokines, and to perform phagocytosis of foreign substances (7-9). Neutrophils have been shown to be present in the implant area during the acute stages of inflammation (2nd-3rd days) (4, 10).

Titanium implants are being used as a first choice in neurosurgical operations in recent years. Titanium is preferred due to its low elastic modulus, its resistance to corrosion and its biocompatibility. Titanium (Ti) is used commercially as pure titanium (CpTi) or titanium alloy (1). Titanium alloy is created to improve the performance of titanium. Alloys, such as Ti-6Al-4V ELI (extra-low level of interstitial content), are widely used for medical and dental implant materials. Ti-6Al-4V alloy has a titanium content of 89.9%, an aluminum content of 5.5-6.5%, and a vanadium ratio of 3.5-4.5% (11). Pure titanium and its alloys are oxidized as soon as they contact with air and form an oxide layer of 1-2 nm in thickness, and prevent further redox reaction of metals. Titanium dioxide ($TiO_2$) contributes to the anti-corrosive effect of the implant. Metal hypersensitivity is classified as a type IV hypersensitivity reaction, characterized by a sensitization phase at the first exposure and immune response subsequent to the exposures of sufficient concentrations. To become allergic, metal ions require binding with natural proteins to form antigenic hapten complexes. These complexes are then processed by antigen presenting cells and presented to T cells (12).

Hypersensitivity to metal is common in the general population, most commonly observed in nickel and followed by cobalt and chrome (11). Titanium corrosion (wear) ratio is 0.02 mm/year (13). Titanium and its alloys release Ti ions and also vanadium, aluminum, niobium, molybdenum as a result of the wear (13, 14). Titanium ions could bind to cellular and serum human proteins, particularly transferrin and albumin, and produce haptenic antigens that elicit immune responses (15) and reactive oxygen metabolites are formed (16). Then, particles formed by metal wear are phagocytosed by macrophages. This increases the release of proinflammatory cytokines, impairs the implant-bone alignment, and enhances osteolytic activity(17). Titanium ions also increase bone destruction by inducing osteoclasts (18). Metal wear disrupts the surface of $TiO_2$, allowing the formation of highly oxidized product and leading the tissues surrounding the implant to turn black (15). Titanium levels were found to be high in patients with failed or rejected implants (12, 19).

### Natural Immunity

Macrophages could be polarized by "classical" (M1) and "alternative" (M2) activation by cytokines. In contrast to IFN-γ induced macrophages (M1) with proinflammatory and antimicrobial activity, M2 macrophages are stimulated with IL-4.

Cytokines could be broadly grouped according to their pro- (TNF-α, IL-1β, IL-6, etc.) and anti-inflammatory (IL-1Rα, IL-10, and TGF-β) functions. Macrophages may release both types of cytokines depending on their activation inducers. TNF-α, IL-1β, and IL-6 are defined as proinflammatory cytokines and play a role in the acute phase of inflammation.

The particles formed due to metal corrosion produce proinflammatory cytokines and growth factors after being identified by macrophages and fibroblasts (TNF-α, IL-1α, IL-1β, IL-6, IL-8, IL-11, IL-15, TGF-α, GM-CSF, M-CSF, PDGF, and epidermal growth factor) (20, 21). These inflammatory factors induce osteolysis by increasing osteoclast formation via RANKL/RANK/OPG (22, 23).

**Adaptive Immune Responses**

Lymphocytes also play an essential role in the peri-implant "rash-reactivity" environment. It is well known that T and B lymphocytes are present in peri-implant tissues (24, 25). Macrophages activate TH1 cells. Some studies using mRNA detection instead of tissue immunohistochemistry (IL-2) have shown increased expression of TH1 cytokines (26). Macrophages and lymphocytes interact with each other through co-receptors and cytokines (27). These TH responses were characterized as type IV delayed type hypersensitivity. Sensitized by metal-antigen and activated DTH T cells secrete various cytokines that activate macrophages (21). For example, IL-3 and GM-CSF induce hematopoiesis of granulocytes; monocyte chemotactic activating factor (MCAF) induces the chemotaxis of monocytes; IFN- y and TNF-β activate endothelial cells that facilitate infiltration, and the migration inhibitory factor (MIF) signals macrophages to keep the DTH reaction in the local area. Active macrophages increase the ability to deliver MHC II and IL-2 and trigger activation of more T-DTH cells, which activates more macrophages, resulting in further activation of the T-DTH cells. DTH could cause extensive tissue damage with self-sustaining response (21)

**Diagnostic Tests**

Diagnostic tests for titanium allergy include epicutaneous patch testing, intradermal tests, lymphocyte transformation test (LTT), lymphocyte migration inhibition, triple test, and bi-digital o ring test (BiDORT).

The patch testing is the test used for the type IV hypersensitivity reaction. The positivity of patch testing for titanium is very insufficient because TiO2 cannot pass healthy skin and react (28). A negative test does not exclude the presence of a titanium allergy.

Lymphocyte transformation test is a test that measures the in vitro proliferation response of lymphocytes following antigen-specific activation. With this test, titanium hypersensitivity is measured more positively than patch testing. Some authors reported that the positive results were because the test showed systemic reactions (29).

## 2. Conclusion

Titanium allergy is very rare. If metal hypersensitivity to implants occurs, it is controversial whether metal hypersensitivity causes implant failure or whether implant failure causes metal hypersensitivity.

If the titanium hypersensitivity reaction is proven, the definitive treatment is the removal of the device. Only in some cases, medical treatment is possible. There is no reliable screening test for hypersensitivity to implants, and further research is needed in the future.

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