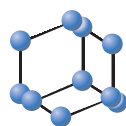
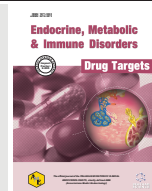


LETTER TO THE EDITOR

BENTHAM
SCIENCE

Immunogenicity of Nickel-Further Explored

Mohsen Baghchechi¹ and Sharon E. Jacob^{1,2,*}¹School of Medicine, University of California Riverside, Riverside, CA, USA; ²Section of Dermatology, Loma Linda Veteran's Health Administration, Loma Linda, CA, USA

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Abstract: Recent reports of the relationship between nickel, allergy and autoimmunity have been described. However, there remains a lack of information on the concordance between nickel sensitization and potency. Of note, an article by Drenovska *et al.* recommended a call for increased epidemiologic studies to define the prevalence of autoimmune syndromes induced by adjuvants such as nickel-containing metal implants. Accumulating reports of dermatologic manifestations following medical device implantation highlights the need for consideration regarding the potential sequelae following metal implantation. Considering the medical and the functional necessity of certain device materials, the authors agree calling for further epidemiological studies are needed to prevent metal-related autoimmunity, and additionally discover novel testing strategies.

Keywords: Immunology, allergy, nickel, autoimmune, epidemiology, metal implant, hypersensitivity.

1. LETTER TO THE EDITOR

We recently read with great interest the article by Drenovska *et al.*, "Nickel and Skin: From Allergy to Autoimmunity" and concur that adjusted epidemiological studies providing evidence on the prevalence of autoimmune syndromes induced by adjuvants (ASIA) subsequent to implant surgery are needed [1]. With regard to metal implanted devices, the authors' highlight that metal ions, specifically nickel, can serve as haptens with immunological potential [1]. Likewise, cadmium, chromium, palladium and cobalt have also been reported to be sensitizers with pro-inflammatory effects that potentially trigger autoimmunity [2, 3].

The mechanism behind this immunologic potential is multifactorial. Metals are known for their adjuvant properties, in which they require an additional step of endogenous peptide association with dermal cellular matrix proteins in order to target multiple histone compatibility (MHC) proteins on antigen presenting cells and subsequently activate T-Cells [4]. Recent data has shown nickel as capable of directly binding to human Toll-like receptor 4 (TLR4) of dendritic cells and generating a pro-inflammatory effect [5]. As an inflammatory mediator with downstream release of cytokines, nickel induced TLR4 activation may stimulate both innate and adaptive immunogenicity in humans. And yet, direct metal hapten activation via T cell receptors has alternatively been described [6], with aberrant peptide processing potentially activating T cell self-peptides, and possibly inducing autoimmunity [7]. Of interest, Rachmawati *et al.* studied the association between thyroid autoantibodies

and metal hypersensitivity and a relative inverse association between metal hypersensitivity and autoimmune thyroiditis, which may suggest an indirect protective mechanism based on competing immune responses [8]. Evidence for a mixed immune response is further supported by the observed modulating effect of interleukin-4 and interferon-gamma on the survival and function of pro-allergic effector cells, whereby nickel exposed T cells from peripheral blood favors Th1 cytokine release, while dermal T cells exhibit a Th2 phenotype, illustrating the heterogenous response to nickel [9, 10].

The lack of concordance between sensitization and potency in regard to nickel-induced allergy among mammalian species warrants further discussion. Basketter notes evidence that nickel is a weak sensitizer with low potency, in experimental Guinea pig models, while in humans nickel may behave as a moderate sensitizer [11]. These studies highlight potential differences in sensitizing (prolonged) exposures to high release nickel and/or the possibility that specific receptors in human skin could impact the development of nickel allergy. It is notable that prolonged exposure is defined as 10 minutes of cutaneous exposure on three or more occasions within 2 weeks, or 30 minutes on one or more instances in a two-week period of time, which has been shown to be critical to sensitization and correlates with the observed association with body piercings.

The relationship following medical device implantation however is less clear. Alternative testing strategies are needed because metal induced autoimmunity has been reported in individuals that did not test positive on pre-implantation patch testing, who have had dramatic improved clinical response to removal and replacement of the suspect implant [12]. This again underscores the 'unpredictable' immunologic response to nickel and the need for further epidemiologic

*Address correspondence to this author at the School of Medicine, University of California Riverside, Riverside, CA, USA; Tel: 9097821961; E-mail: mohsen.baghchechi@medsch.ucr.edu

logic studies to shed light on metal-associated immune responses.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflict of interest, financial or otherwise.

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