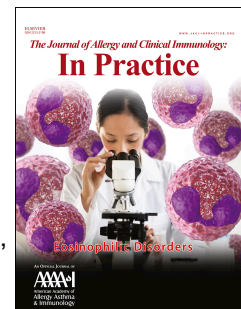


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When Joints Fail: Identifying the Allergen Helps

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Over 1 million joint replacement surgeries are performed each year in the US and failure occurs in 10% of them, raising major health and economic burdens (1). The reasons for failure are multiple and include malposition, infection and hypersensitivity/allergy to implant components. The term “hypersensitivity”, defining an inflammatory reaction to the implant components, is more appropriate than the term “allergy,” since the implant-induced inflammation can be mediated by innate or adaptive immunity. Implant hypersensitivity (HS), also sometimes called “adverse reaction to metal debris” or “pseudotumor-like periprosthetic tissue reactions” in the specific condition or metal on metal hip replacement, undoubtedly exists but it cannot be stated to always be an allergic reaction. Innate HS, also referred to as non-allergic HS, may develop in response to the generation of metal/polymer wear debris that causes local inflammation due to activation of macrophages, thus leading to osteoclast triggering, bone resorption and implant loosening. There is no diagnostic test for non-allergic HS. Conversely, adaptive HS, i.e. allergy to prosthesis, also called type IV HS, is mediated by specific T cells that infiltrate the peri-implant tissue where they are activated by antigen-presenting cells. The main allergens are metals (nickel, chromium, cobalt) and bone cement compounds. T cell activation leads to the recruitment of leucocytes that will cause joint inflammation, pain and loosening.

The pathophysiology of implant HS is not well understood. Recent studies analyzing the peri-implant tissue of failed metal-on-metal hip arthroplasty showed that the composition of inflammatory cells was polarized to either macrophages or T-lymphocytes (2)(Paukkeri EL, 2016). Macrophage, but not T cell-dominated inflammation was associated with high blood metal concentrations and increased production of IL-6 and TNF α by implant infiltrating cells. More recently, experimental studies demonstrated that orthopedic implant debris activates the NLRP3 inflammasome leading to a type 17/Th17 inflammation (3)(Samelko L, 2019). This profile is compatible with an innate immune reaction to wear debris that is ingested by macrophages, leading to their activation. Conversely, T cell-dominated inflammation, also called aseptic lymphocyte-dominated vasculitis associated lesion (ALVAL), is characterized by the aggregation of T cells around post-capillary venules; whereas

macrophages are poorly represented (3,4)(Paukkeri EL, 2016; Thomas P, 2009). When analyzed more in depth in one case report, these T cells were clonally expanded and produced IFN γ , compatible with an adaptive type1/Th1 immune reaction (5)(Thomas P, 2000).

The diagnosis of type IV allergy to implants is still very difficult to confirm for two main reasons: (i) analysis of the peri-implant tissue or of the joint fluid is not routinely performed to confirm the presence of an inflammatory reaction compatible with a type IV HS reaction; (ii) circulating/blood biomarkers for peri-implant immune reactions are lacking. Therefore, the diagnosis of implant allergy relies on the presence of surrogate markers, which define systemic sensitization to implant components especially to metals and more specifically to nickel. Epicutaneous patch tests (as performed in the diagnosis of allergic contact dermatitis) and blood immunobiological assays (such as the lymphocyte transformation test – LTT) are used to test for the presence of specific T cells in patients. However, being sensitized, i.e. harboring joint compound-specific T cells, does not imply clinically pertinent allergic reaction in the implanted joint. Moreover, the validity of patch testing as a method to determine implant HS is questionable, since the immunopathology of allergic contact dermatitis is likely to differ from that of peri-implant HS. Finally, recent data provide strong information on the lack of correlation between the sensitization status and the ability to develop an allergic reaction, the more so since most normal individuals are sensitized, but not allergic, to metals (6)(Bechara et al, 2019). In this context, it is not surprising that pre-implant screening for sensitization to metals or cement is not recommended, since it has no predictive value for the success or failure of the surgery. Indeed, several studies (reviewed in a meta-analysis (7)) showed that, although the frequency of sensitization to metals increases significantly after joint replacement, patch testing was not able to discriminate between stable and loose implants (7-9)(Granchi et al, 2012; Munch HJ, 2015; Middleton S, 2016). There is, however, one exception, the existence of a history of allergic contact dermatitis to metals, which may have to be confirmed by patch testing, because of a 4 fold increased risk of joint replacement failure in these patients (10)(Granchi 2008).

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78 In this issue, the study of Mayer AS et al. (1) brings new and important practical information on the
79 topic (Mayer AS et al, 2021). It confirms that sensitization to implant components is associated with
80 joint replacement failure. However, more importantly, it shows that in patients with implant failure
81 symptoms suggestive of implant HS, identification of the allergens and revision to non-allergenic
82 materials improves outcomes. The study enrolled 105 joint failure patients (85 knees, 18 hips and 2
83 shoulders) referred by their orthopedic surgeon after exclusion of infection and mechanical causes
84 for failure. Sensitization was assessed by patch-testing to metals and bone cement and by a Nickel
85 lymphocyte proliferation test. Sixty-one patients (59%) were sensitized to a joint replacement
86 component of their implant and 44 patients were not. Patients underwent revision surgery and 67 of
87 them could be contacted 9 to 12 months later to assess their outcomes. Patients sensitized to metals
88 were revised to a titanium or oxinium alloy implant and patients sensitized to bone cement were
89 revised to a press-fit option. Among the 35/67 patients with implant sensitization, 22 were revised
90 with a prosthesis devoid of the sensitizer whereas 13 patients were not revised. Overall
91 improvement was noted in 16/22 revised versus 1/13 non-revised patients, with significant
92 differences in specific symptom improvement following revision. Those who were revised due to
93 implant sensitization were significantly more likely to report no or mild pain, no or mild swelling, no
94 or mild instability, with a trend towards a better range of motion. Interestingly, non-sensitized
95 patients also improved after implant revision, although to a lesser extent than sensitized patients, as
96 previously observed (11)(Zondervan, 2019). Therefore, testing for sensitization is of value in implant
97 failures, compatible with the diagnosis of implant HS if revision is planned.

98 In summary, testing with the implant allergens could be useful : (i) before implant surgery, in patients
99 with a medical history of metal contact dermatitis; (ii) before revision, in patients with implant failure
100 symptoms suggestive of implant HS. If the sensitivity is confirmed, use of an implant devoid of the
101 offending allergens strongly improves the outcome.

Diagnosis of implant HS is of paramount importance. As stated above, implant HS may be allergic, involving specific T cells, or non-allergic, mediated by the activation of innate immunity. In both cases, the peri-implant inflammation may lead to implant failure. Therefore looking for sensitization addresses only one part of the problem. New diagnostic tools for hypersensitivity to implants are needed. This requires characterization of the features of local inflammation (type 1, type 2, type 17) and identification, in the case of allergic HS, of the responsible allergen. This information will make it possible to better manage patients in the event of a revision and/or to provide targeted anti-inflammatory treatment in the case of revision failure.

Bibliography

1. Mayer AS, Erb S, Kim RA, Dennis DA, Shirname-More L, Pratte KA, Barker EA, Maier LA, Pacheco KA. Sensitization to implant components is associated with joint replacement failure; identification and revision to non-allergenic hardware improves outcomes. *J ALLERGY CLIN IMMUNOL PRACT*. 2021; this issue
2. Paukkeri EL, Korhonen R, Hämäläinen M, Pesu M, Eskelinen A, Moilanen T, Moilanen E. The Inflammatory Phenotype in Failed Metal-On-Metal Hip Arthroplasty Correlates with Blood Metal Concentrations. *PLoS One*. 2016;11:e0155121. doi: 10.1371/journal.pone.0155121.
3. Samelko L, Caicedo MS, Jacobs J, Hallab NJ. Transition from metal-DTH resistance to susceptibility is facilitated by NLRP3 inflammasome signaling induced Th17 reactivity: Implications for orthopedic implants. *PLoS One*. 2019;14:e0210336.
4. Thomas P, Braathen LR, Dörig M, Auböck J, Nestle F, Werfel T, Willert HG. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy*. 2009 Aug;64(8):1157-65. doi: 10.1111/j.1398-9995.2009.01966.x.
5. Thomas P, Thomas M, Summer B, Naumann T, Sander CA, Przybilla B. Intolerance of osteosynthesis material: evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and TH1-type cytokine expression in the periimplantar tissue. *Allergy* 2000;55:969–972.
6. Bechara R, Pollastro S, Azoury ME, Szely N, Maillère B, de Vries N, Pallardy M (2019) Identification and characterization of circulating naïve CD4+ and CD8+ T cells recognizing Nickel. *Front. Immunol*. 2019; 10:1331.doi: 10.3389/fimmu.2019.01331
7. Granchi D, Cenni E, Giunti A, Baldini N. Metal hypersensitivity testing in patients undergoing joint replacement: a systematic review. *J Bone Joint Surg Br*. 2012;94:1126-34. doi: 10.1302/0301-620X.94B8.28135.
8. Münch HJ, Jacobsen SS, Olesen JT, Menné T, Søballe K, Johansen JD, Thyssen JP. The association between metal allergy, total knee arthroplasty, and revision: study based on the Danish Knee Arthroplasty Register. *Acta Orthop*. 2015;86:378-83.
9. Middleton S, Toms A. Allergy in total knee arthroplasty: a review of the facts. *Bone Joint J*. 2016;98-B:437-41. doi: 10.1302/0301-620X.98B4.36767.
10. Granchi D, Cenni E, Tigani D, Trisolino G, Baldini N, Giunti A. Sensitivity to implant materials in patients with total knee arthroplasties. *Biomaterials*. 2008;29:1494-500. doi: 10.1016/j.biomaterials.2007.11.038
11. Zondervan RL(1), Vaux JJ(2), Blackmer MJ(2), Brazier BG(3), Taunt CJ Jr(2). Improved outcomes in patients with positive metal sensitivity following revision total knee arthroplasty. *J Orthop Surg Res*. 2019 Jun 17;14(1):182. doi: 10.1186/s13018-019-1228-4.