BJD
British Journal of Dermatology

Hypersensitivity reactions from metallic implants: a future challenge that needs to be addressed

DOI: 10.1111/j.1365-2133.2009.09526.x

Prolonged or repeated skin exposure to jewellery, buttons, clothing fasteners, mobile phones and leather may result in metal sensitization. Also, oral exposure to dental restorations may lead to cobalt or gold sensitization. It is estimated that up to 17% of women and 3% of men are nickel sensitized and that 1–3% are sensitized to cobalt and chromate.[1] Regulatory interventions have proven successful in decreasing the prevalence of contact sensitization and allergic contact dermatitis (ACD), e.g. nickel sensitization and dermatitis have decreased significantly among ear-pierced women following the Danish nickel regulation.[2]

In its acute form, ACD is characterized by pruritus, erythema, papules and possibly vesicles whereas chronic ACD may be dry, scaly and fissured. In rare instances, localized or generalized eruptions mimicking ACD may be seen in patients on their skin overlying the site of a metallic implant.[3] Localized eruptions are typically associated with static implants such as plates, nails, screws, endovascular devices (stents, abdominal aortic aneurysm endografts and patent foramen ovale occluders) and pacemakers, whereas they rarely occur in association with dynamic joint prostheses. If a patient displays a strong positive patch test reaction to one of the metals in the alloy, implant removal will often result in resolution of their eruption.[3] Generalized eruptions due to nickel release (μg) from small metallic eyelets at the base of polyurethane peripheral intravenous catheters have been observed.[4] This underscores that low systemic nickel concentrations may activate the immune system.

Subjects with or without metal sensitization may also develop other unwanted delayed-type hypersensitivity reactions following insertion of metallic implants. In the 1960s and 1970s, the early prostheses used for total hip arthroplasty were metal-on-metal. Their use was gradually abandoned (and replaced by metal-on-polyethylene prostheses) as they resulted in release of cobalt and chromium into the blood, hair and urine as well as metal sensitization and prosthesis loosening.[5,6] Recently, second-generation metal-on-metal bearings have become popular following substantial improvements in manufacturing. However, there is again increasing evidence and concern about the biological consequences of metal release from such bearings. A review found that the prevalence of metal sensitization was approximately 25% among patients with well-functioning hip arthroplasties and 60% among patients with a failed or a poorly functioning implant.[7] Although these prevalences are much higher than general population estimates,[1] it remains unknown whether metal sensitization causes implant failure or implant failure causes metal sensitization. Furthermore, most intracoronary stents are made from stainless steel containing nickel, chromium and molybdenum. It has been suggested that nickel sensitization is one of the triggering factors of in-stent restenosis[8,9] although other studies have rejected an association.[10] Finally, it has been shown that the risk for restenosis was increased threefold in gold-sensitized patients who had gold-plated stents inserted.[11]

Life expectancy is increasing. The demographic change will inevitably result in an increased use of metallic implant devices. In the U.S.A., the number of primary total hip and knee arthroplasties inserted each year between 1990 and 2002 increased from 119 000 to 193 000 and from 129 000 to 381 000, respectively.[12] If the association between metal allergy and device failure is not addressed now, in the future it will possibly result in increasing health care costs as well as morbidity in affected patients. At present, we cannot predict which patients will develop hypersensitivity reactions following insertion of metallic implants. It is generally agreed that patch test screening prior to insertion of metallic implants is not recommended unless the patient has had previous allergic reactions to metallic implants. Furthermore, there is no convincing evidence to support that subjects with previous metal sensitization are at greater risk of developing hypersensitivity reactions following implantation of metallic devices than individuals without metal sensitization. However, there are some case reports describing metal allergy and metal implant failure in subjects who report antecedent ACD from, for example, jewellery exposure. Although it has been shown that the sensitization and elicitation threshold concentrations of ACD vary between individuals,[13,14] it is unknown whether those who report, for example, jewellery dermatitis also are at greater risk of developing device failure. Finally, it is speculative whether regulatory interventions used to minimize metal sensitization and ACD in European populations may also protect future generations from developing hypersensitivity reactions from metallic implants. If so, an effect will be noted only in several decades, when the people now young and protected by nickel regulation will age and need metal implants. Until then, i.e. in the next few decades, the problem will even be more acute, as the now middle-aged (women) who have been sensitized to a large extent will increasingly require implant surgery.[2,15–17]

There is a clear need for randomized, prospective studies to evaluate the association between metal sensitization, device failure and metal release. Also, there is a need for immunological and genetic characterization of individuals who develop metal implant failure due to hypersensitivity reactions. Apparently, only a minority develops metal sensitization and device failure. Manufacturers should develop clinically relevant *in vitro* methods that predict corrosion as well as alloys that do not release metal ions or particles. Although biocompatible metals such as titanium rarely result in metal hypersensitivity, their higher costs have restricted their use to high-risk patients and those with previous complications. Although it is clearly unnecessary and may be economically disadvantageous to use such inert metals in most patients, until there is greater understanding perhaps this is the safest course?

Department of Dermato-Allergology, J.P. Thyssen
National Allergy Research Centre, J.D. Johansen
Gentofte Hospital, T. Menné
University of Copenhagen, C. Lidén*
DK-2900 Hellerup, Denmark M. Bruze†
Institute of Environmental Medicine, I.R. White‡
Karolinska Institutet,
SE-171 77 Stockholm, Sweden
†*Department of Occupational and Environmental Dermatology,*
Malmö University Hospital, Lund University,
SE-205 02 Malmö, Sweden
‡*Department of Cutaneous Allergy,*
St John's Institute of Dermatology,
London SE1 7EH, U.K.
E-mail: jacpth01@geh.regionh.dk

References

1 Thyssen JP, Linneberg A, Menné T *et al.* The epidemiology of contact allergy in the general population – prevalence and main findings. *Contact Dermatitis* 2007; **57**:287–99.
2 Thyssen JP, Johansen JD, Menné T *et al.* Nickel allergy in Danish women before and after nickel regulation. *N Engl J Med* 2009; **360**:2259–60.
3 Gawkrodger DJ. Nickel sensitivity and the implantation of orthopaedic prostheses. *Contact Dermatitis* 1993; **28**:257–9.
4 Raison-Peyron N, Guillard O, Khalil Z *et al.* Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter. *Contact Dermatitis* 2005; **53**:222–5.
5 Coleman RF, Herrington J, Scales JT. Concentration of wear products in hair, blood, and urine after total hip replacement. *Br Med J* 1973; **1**:527–9.
6 Benson MK, Goodwin PG, Brostoff J. Metal sensitivity in patients with joint replacement arthroplasties. *Br Med J* 1975; **4**:374–5.
7 Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001; **83A**:428–36.
8 Iijima R, Ikari Y, Amiya E *et al.* The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol* 2005; **104**:319–25.
9 Koster R, Vieluf D, Kiehn M *et al.* Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000; **356**:1895–7.
10 Hillen U, Haude M, Erbel R *et al.* Evaluation of metal allergies in patients with coronary stents. *Contact Dermatitis* 2002; **47**:353–6.
11 Svedman C, Ekqvist S, Moller H *et al.* A correlation found between contact allergy to stent material and restenosis of the coronary arteries. *Contact Dermatitis* 2009; **60**:158–64.
12 Kurtz S, Mowat F, Ong K *et al.* Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J Bone Joint Surg Am* 2005; **87**:1487–97.
13 Fischer LA, Menné T, Johansen JD. Experimental nickel elicitation thresholds – a review focusing on occluded nickel exposure. *Contact Dermatitis* 2005; **52**:57–64.
14 Uter W, Fuchs T, Hausser M *et al.* Patch test results with serial dilutions of nickel sulfate (with and without detergent), palladium chloride, and nickel and palladium metal plates. *Contact Dermatitis* 1995; **32**:135–42.
15 Schnuch A, Uter W. Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 2003; **49**:107–8.
16 Thyssen JP, Johansen JD, Carlsen BC, Menné T. Prevalence of nickel and cobalt allergy among female patients with dermatitis before and after Danish government regulation: a 23-year retrospective study. *J Am Acad Dermatol* 2009; **61**:799–05.
17 Thyssen JP, Jensen P, Carlsen BC *et al.* The prevalence of chromium allergy in Denmark is currently increasing as a result of leather exposure. *Br J Dermatol* 2009; **161**:1288–93.

