Journal Name	Manuscript No.	Dispatch: 9.4.03	Journal: BJD	CE: Blackwell
BJD	5404 B	Author Received:	No. of pages: 5	PE: Mohana

British Journal of Dermatology 2003; **148:** 1–5.

TOPICAL REVIEW

Metal sensitivities and orthopaedic implants revisited: the potential for metal allergy with the new metal-on-metal joint prostheses

D.J.GAWKRODGER

Department of Dermatology, Royal Hallamshire Hospital, Sheffield S10 2JF, U.K.

Accepted for publication 19 January 2003

Summary The potential of metal-containing orthopaedic prostheses to induce problems through metal allergy taxes dermatologists and orthopaedic surgeons alike. Metal-on-plastic joint replacements are not thought to induce metal allergy but wear products, principally polypropylene particles, produce a foreign body reaction in bone and may lead to aseptic loosening of the joint. Orthopaedic surgeons are increasingly using metal-on-metal joint replacements, particularly for younger patients, as some evidence suggests that there is less wear debris and hence less aseptic loosening. The original metal-on-metal hip joints of the 1960s were associated with sensitivities to cobalt, nickel and chromate when loosening occurred. The potential for modern metal-on-metal joint prostheses, with their lower production of wear debris, to sensitize the recipient to metals or to induce a problem in subjects already allergic to metals, is unclear. One uncontrolled series suggested an association between nickel allergy and prosthesis loosening in some subjects, but the question has yet to be addressed in a prospective study and to date there is no other observation in the orthopaedic literature to suggest a problem.

Key words: aseptic loosening, chromate, cobalt, joint replacement, nickel allergy, orthopaedic surgery, polypropylene, prostheses

Static metal implants for fractures, for example the AO system, were introduced in the 1950s. The first prosthetic joint was the replacement hip pioneered by Charnley and first used in 1962. The initial prostheses were metal-on-metal and there was high frictional wear that produced particulate deposition in the tissues around the joint. At first, Vitallium (chrome, cobalt, molybdenum with a trace of nickel) was used; later, stainless steel was employed. Frictional wear resulted in loosening of the joint in about a quarter of cases. There was release of nickel, chromium and cobalt ions into the joint and tissues.

Correspondence: David Gawkrodger. E-mail: david.Gawkrodger@zsth.nhs.uk

Early metal-on-metal prosthetic hips and metal sensitization

With the early metal-on-metal joints, postoperative patch testing in one series demonstrated that 28% of subjects were metal allergic.[1] Among subjects who had loosening of the prosthetic joint, the prevalence of metal allergy demonstrated by patch testing was raised, although it varied between studies, with quoted figures of 74%,[2] 46%[3] and 13%.[4] The commonest allergen was cobalt followed by nickel then chromate.

The implication is that either the sensitization played a part in the failure of the prosthesis or that the loosening resulted in release of metal ions that induced the metal allergy. Either or both explanations are possible and it is unfortunate that the answer to this question is still unclear as it is of considerable importance to understanding the mechanism of loosening and for giving appropriate advice for patients with metal allergies.

Metals used in orthopaedics

Several metal alloys are used in orthopaedics. Vitallium is composed of cobalt 70%, chromium 25–30% and molybdenum 5–7%, with a trace of nickel. The alloys of cobalt–chromium–tungsten–nickel and cobalt–chromium–molybdenum contain 9–11% and 2% nickel, respectively. Austenitic stainless steel is a commonly used alloy and contains nickel 8·5–14% (up to 35%), chromium 17–20%, molybdenum 2–3%, with manganese and less than 1% carbon, nitrogen, silicon, sulphur, phosphorus and niobium. When titanium is used for an orthopaedic prosthesis, sometimes the pure metal is employed but aluminium (6%) or vanadium (4%) can be added to improve the tensile properties.

Composition of prosthetic hips

Hip replacements with a metal femoral component and a plastic acetabular part were introduced in the 1960s following the problems experienced with the original hips and have continued to be employed up to the present day. Current metal-on-plastic hips consist of an austenitic stainless steel femoral shaft and head with a high molecular weight polyethylene acetabular cup. The prosthesis is cemented using methyl methacrylate bone cement in more elderly patients but in younger patients porous coated implants are used that do not require cementing, although these have a higher risk of loosening. Prostheses with ceramic or carbon fibre acetabular cups or heads are available. Trochanteric restriction wires are sometimes used; these may have a nickel content of 14% and may be more likely to release nickel than the stainless steel of the prosthesis.

Complications of hip replacement

The short-term problems of hip replacement are dislocation, sciatic nerve damage and infection. The longer-term complications are mechanical failure due to aseptic loosening, a weak bone–prosthesis bond and wear product deposition. Particle shedding results from abrasion between the high molecular weight polyethylene cup and the metal femoral ball: a width of 0·2 mm per year can be lost from the polyethylene surface.[5] Abraded wear particles give rise to a foreign body reaction in the adjacent bone, leading to osteolysis which after a few years can result in aseptic loosening of the prosthesis.

A patient whose prosthesis is loosening may complain of pain on walking and rotation of the leg. There may be radiolucency around the prosthesis on X-ray and biopsy of the adjacent joint can show a foreign body reaction to the detached polyethylene or metal wear particles (even when there is no suggestion of allergy).

Cutaneous reactions to orthopaedic implants

High sulphur (0·3%) stainless steel AISI 303 can release sufficient nickel (1·5 μg cm^{-2} per week) to induce dermatitis in some nickel-sensitive subjects.[6,7] Low sulphur (0·03%) stainless steel does not induce dermatitis in nickel-allergic subjects (nickel release 0·03 μg cm^{-2} per week) and should be used for orthopaedic implants.

There is one prospective study of 48 subjects who were patch tested before and 1 year after receiving a static orthopaedic implant of stainless steel for extremity fractures.[8] The authors showed no problems in the three nickel-allergic subjects (they were still nickel-sensitive 12 months later) and no development of metal allergy in the other 45. Despite this, the development of a localized eczema over a static metal prosthesis, e.g. a tibial plate, or over screws or a hip joint, is well described although uncommon.[9–11] Occasionally a generalized eczematous or urticarial reaction is observed.[12,13]

In a study of 18 subjects followed for a mean of 6 years who had received a joint replacement (or static implant) containing a metal to which they were known to be allergic by patch testing, mechanical failure occurred in two, 'new' eczema after surgery was seen in three, eczema disappeared in three and existing dermatitis remained constant in seven.[14] Proof of any association in instances of persisting eczema is provided by demonstrating that patch tests are positive and observing the clearance of the eruption if the prosthesis is removed.

Studies of sensitization after or before and after hip replacement

There have been few prospective studies of metal allergies before and after joint replacement. Studies using patch tests to define metal allergy have shown sensitization rates after hip replacement to be low and not to be associated with failure of the prosthesis nor the development of eczema over the times of study (generally only a year or two). Metal sensitization was induced in three (one nickel, two cobalt) of 112,[15] eight (two nickel, five cobalt, one chromate) of 85[16]

and four (three nickel, one cobalt) of 66.[4] A large study from the Cleveland Clinic looking at cutaneous reactions among 1400 patients receiving joint replacements and 200 undergoing internal fixation revealed six subjects in whom there was a transient exanthem (one was patch test positive to nickel) and 13 who had persistent eczema, of whom two were positive to a metal on patch testing.[17] Three subjects had loosening of their prosthesis over the period of the study and all were negative on patch testing.

There are only three studies in which patch testing was performed before and after metal-on-plastic hip replacement. The first showed that the number of patients reacting in patch tests afterwards was lower than before: one persisted in being positive to nickel and cobalt, and five of 69 subjects patch tested, who had previously been positive to nickel, cobalt or chromium, became negative.[18] This suggests that the process of insertion of a prosthesis may actually induce immunological tolerance. No subject had loosening, although the follow-up period of 7 months was quite short. The second report of 85 cases describes loosening in 10 (mean follow-up 17 months), none of whom was metal-allergic on patch testing, although there were nine cases of possible sensitization by prosthesis (four cobalt, two methyl methacrylate, one nickel, one nickel and cobalt, one chromium) without any reported cutaneous reaction.[16]

In the third study, of 128 subjects undergoing hip replacement, 12 were positive to a metal before replacement (only six were positive afterwards, none of whom had eczema or loosening), and 20 were positive to a metal afterwards on patch testing, of whom three had eczema and one had loosening.[19] Of those with negative patch tests postreplacement, five had loosening. The conclusion was that induction of metal allergy was observed but was uncommon.

Overall experience with metal-on-plastic hip replacement

The overall experience with metal-on-plastic hips suggests that skin reaction and joint loosening are uncommon in known nickel-allergic subjects who receive a hip replacement[20] and that, unlike in the original metal-on-metal hips, metal allergy is not a common accompaniment or cause of prosthesis failure. Indeed, the use, without cutaneous problems or loosening, of stainless steel metal-on-plastic hip prostheses when pre-existing nickel or other metal allergy is known, is well described.[13,14,16,18,19] However, in the light of the occasionally reported case, it might be wise to advise caution for patients known to be nickel-allergic preoperatively, and to suggest the use of a hip that will release the lowest amount of nickel while providing appropriate function, especially as a failure rate of 10% or more can be expected anyway.

Problems with replacements of other joints

Knee replacement is, after hip, the next most common prosthesis insertion. The knee replacements currently used have a titanium alloy femoral surface and an ultra-high molecular weight polyethylene patellar and tibial surface. Failure of the prosthesis, e.g. of the patellar component, is associated with an increase in the titanium, nickel, cobalt and chromium content of the synovial fluid and with an increase in serum levels of titanium.[21,22] Although increased levels of metal ions in the joint might theoretically predispose to induction of allergy, there are no reports of rashes or of metal allergy being associated with failure of a knee prosthesis. The failed prosthesis shows osteolysis of the surrounding bone on X-ray and deposition of titanium, cobalt, chromium and polyethylene in the synovium with a foreign body reaction on histology.[23–25]

New metal-on-metal hip replacements

Metal-on-metal hips, typically with a cobalt alloy femoral stem and a titanium acetabular cup, were reintroduced in the 1980s. They have the advantage of producing less abrasive wear than metal-on-plastic prostheses, namely a depth loss of 0·1–10 μm per year for the ball and 0·2–6 μm per year for the cup.[5] The metal particles produced are smaller than the polyethylene ones from plastic-on-metal prostheses and are said to induce less tissue reaction and, hence, less osteolysis.[5] These hips are most appropriate for younger subjects in whom they are inserted without cement. None the less, even in a normally functioning metal-on-metal hip there is some systemic release of metal as serum levels of cobalt, titanium and chromium are increased (the latter two on average threefold and fivefold higher, respectively) 3 years after insertion.[26,27]

Outcomes after metal-on-metal hip replacement

The general outcome studies on metal-on-metal hips so far reported have shown mostly good results. One study

revealed that at 6 months to 4 years, 70 of 74 subjects had a good or excellent result and there was no loosening or osteolysis.[28] Another report of 78 cases at 5-year follow-up revealed no 'metallosis' in three patients who required further surgery (one for late infection and two for ectopic ossification), and no excess of problems,[5] whereas an earlier investigation, of 154 subjects over 5–12 years of follow-up, found that revision because of loosening was needed in 15, with four having 'gross metal reaction'.[29]

There is just one follow-up study that has looked at the problem of metal sensitivities and prosthesis failure in patients receiving metal-on-metal hip replacements.[30] Over a period of 5 years (to 2001) in an orthopaedic unit, metal-on-metal hip replacements were performed in 200 patients of whom five had prosthesis failure due to loosening. These subjects, together with 18 randomly selected patients from the series (who did not have loosening), were patch tested to nickel, cobalt and chromate using TRUE test (Pharmacia, Uppsala, Sweden). Three of the five who had loosening were positive on patch testing, all to nickel, compared with three who were patch test positive to metals among the 18 controls. This study raises the possibility of an association of metal allergy with failed metal-on-metal hip prosthesis, but the numbers are too small and it was not sufficiently controlled to allow any definite conclusion to be drawn. A prospective study with patch testing before and after joint replacement, and correlation of the results to prosthesis failure, is required.

Conclusions and the need for further study

Experience from the 1960s and early 1970s with the early metal-on-metal hips indicates that sensitization did occur with the metal-on-metal prostheses used at that time. The studies in the 1970s and 1980s on subjects receiving the metal-on-plastic hips suggested that these joint replacements could be used in patients with known sensitivities to metals and even that immunological tolerance to metals actually might be induced by the introduction of these prostheses. At the present time, metal-on-metal joint replacements are being used by orthopaedic surgeons in patients who are younger than average and who may well require further surgery in the future.

The follow-up studies on metal-to-metal replacement hip joints conducted so far report, at worst, a loosening rate of about 10%, but have not commented on whether cutaneous reactions are observed. Similarly, the question of sensitization to metals and how this might relate to the observed loosening has not been formally assessed. The potential immunological consequence of the presence of the new metal-on-metal implants needs to be defined and related to any failure of the prosthesis. Until these questions are specifically examined it is not possible to be confident that there is no problem with regard to sensitization to metals just because no such cases have been reported to date. It may well be that there is no cause for concern, but past experience suggests that this needs to be demonstrated rather than assumed.

References

1 Benson MKD, Goodwin PG, Brostoff J. Metal sensitivity in patients with joint replacement arthroplasties. *Br Med J* 1975; **4**: 374–5.

2 Elves MR, Wilson JN, Scales JT, Kemp HBS. Incidence of metal sensitivity in patients with total hip replacement. *Br Med J* 1975; **4**: 376–8.

3 Munro-Ashman D, Miller AJ. Rejection of metal to metal prosthesis and skin sensitivity to cobalt. *Contact Dermatitis* 1976; **2**: 65–7.

4 Deutman R, Mulder TJ, Brian R, Nater JP. Metal sensitivity before and after total hip arthroplasty. *J Bone Joint Surg Am* 1977; **59**: 862–5.

5 Wagner M, Wagner H. Medium-term results of a modern metal-on-metal system in total hip replacement. *Clin Orthop* 2000; **379**: 123–33.

6 Menné T, Brandrup F, Thestrup-Pedersen K *et al.* Patch test reactivity to nickel alloys. *Contact Dermatitis* 1987; **16**: 255–9.

7 Haudrechy P, Foussereau J, Mantout B, Baroux B. Nickel release from nickel-plated metals and stainless steels. *Contact Dermatitis* 1994; **31**: 249–55.

8 Hindsen M, Carlsson AS, Moller H. Orthopaedic metallic implants in extremity fractures and contact allergy. *J Eur Acad Dermatol Venereol* 1993; **2**: 22–6.

9 Foussereau J, Laugier P. Allergic eczemas from metallic foreign bodies. *Trans St Johns Hosp Dermatol Soc* 1966; **52**: 220–5.

10 Roed-Petersen B, Roed-Petersen J, Jorgensen KD. Nickel allergy and osteomyelitis on a patient with metal osteosynthesis of a jaw fracture. *Contact Dermatitis* 1979; **5**: 108–12.

11 McKenzie AW, Aitken CVE, Ridsdill-Smith R. Urticaria after insertion of Smith-Petersen Vitallium nail. *Br Med J* 1967; **4**: 36.

12 Barranco VP, Solomon H. Eczematous dermatitis from nickel. *JAMA* 1972; **220**: 1244.

13 Balato N, Costa L, Lembo G *et al.* Allergic contact dermatitis from orthopaedic devices. *Contact Dermatitis* 1995; **32**: 314–15.

14 Carlsson A, Moller H. Implantation of orthopaedic devices in patients with metal allergy. *Acta Derm Venereol (Stockh)* 1989; **69**: 62–6.

15 Carlsson AS, Magnusson B, Moller H. Metal sensitivity in patients with metal-to-metal total hip arthroplasties. *Acta Orthop Scand* 1980; **51**: 57–62.

16 Waterman AH, Schrik JJ. Allergy in hip arthroplasty. *Contact Dermatitis* 1985; **13**: 294–301.

17 Kubba R, Taylor JS, Marks KE. Cutaneous complications of orthopedic implants. *Arch Dermatol* 1981; **117**: 554–60.

18 Rooker GD, Wilkinson JD. Metal sensitivity in patients undergoing hip replacement: a prospective study. *J Bone Joint Surg B* 1980; **62**: 502–5.
19 Torok L, Greczy I, Ocsai H, Czako J. Investigation into the development of allergy to metal in recipients of implanted hip prostheses: a prospective study. *Eur J Dermatol* 1995; **5**: 294–5.
20 Burrows D. Is systemic nickel important? *J Am Acad Dermatol* 1992; **26**: 632–5.
21 Jacobs JJ, Siverton C, Hallab NJ *et al.* Metal release and excretion from cementless titanium alloy total knee replacements. *Clin Orthop* 1999; **358**: 173–80.
22 Cracchiolo A, Revell P. Metal concentration in synovial fluids of patients with prosthetic knee arthroplasty. *Clin Orthop* 1982; **170**: 169–74.
23 La Budde JK, Orosz JF, Bonfiglio TA, Pellegrini VD. Particulate titanium and cobalt-chrome metallic debris in failed total knee arthroplasty. A quantitative histologic analysis. *J Arthroplasty* 1994; **9**: 291–304.
24 Berry DJ, Wold LE, Rand JA. Extensive osteolysis around an aseptic, stable, uncemented total knee replacement. *Clin Orthop* 1993; **293**: 204–7.
25 Andersen HN, Ernst C, Frandsen PA. Polyethylene failure of metal-backed patellar components. 111 AGC total knees followed for 7–22 months. *Acta Orthop Scand* 1991; **62**: 1–3.
26 Brodner W, Bitzan P, Meisinger V *et al.* Elevated serum cobalt with metal-on-metal articulating surfaces. *J Bone Joint Surg B* 1997; **79**: 316–21.
27 Jacobs JJ, Skipor AK, Patterson LM *et al.* Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. *J Bone Joint Surg Am* 1998; **80**: 1447–58.
28 Hilton KR, Dorr LD, Wan Z, McPherson EJ. Contemporary total hip replacement with metal on metal articulation. *Clin Orthop* 1996; **329** (Suppl.): S99–105.
29 Andrew TA, Berridge D, Thomas A, Duke RNF. Long-term review of ring total hip arthroplasty. *Clin Orthop* 1985; **201**: 111–22.
30 Antony F, Dudley W, Field R, Holden C. Metal allergy resurfaces in failed hip endoprostheses. *Br J Dermatol* 2001; **145** (Suppl. 59): 48 (Abstr.).

Author Query Form

Journal: BJD

Article: 5404

Dear Author,
During the copy-editing of your paper, the following queries arose. Please respond to these by marking up your proofs with the necessary changes/additions. Please write your answers on the query sheet if there is insufficient space on the page proofs. Please write clearly and follow the conventions shown on the attached corrections sheet. If returning the proof by fax do not write too close to the paper's edge. Please remember that illegible mark-ups may delay publication.

Many thanks for your assistance.

Query reference	Query	Remarks
1	**Au: AO—does this have a definition?**	
2	**Au: Please supply the page range**	

MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

Instruction to printer	*Textual mark*	*Marginal mark*
Leave unchanged	··· under matter to remain	Stet
Insert in text the matter indicated in the margin		New matter followed by
Delete	through matter to be deleted	
Delete and close up	through matter to be deleted	
Substitute character or substitute part of one or more word(s)	/ through letter or through word	New letter or new word
Change to italics	— under matter to be changed	
Change to capitals	≡ under matter to be changed	
Change to small capitals	= under matter to be changed	
Change to bold type	~ under matter to be changed	
Change to bold italic	≈ under matter to be changed	
Change to lower case	Encircle matter to be changed	
Change italic to upright type	(As above)	
Insert 'superior' character	/ through character or where required	under character e.g.
Insert 'inferior' character	(As above)	over character e.g.
Insert full stop	(As above)	
Insert comma	(As above)	
Insert single quotation marks	(As above)	and/or
Insert double quotation marks	(As above)	and/or
Insert hyphen	(As above)	
Start new paragraph		
No new paragraph		
Transpose		
Close up	linking letters	
Insert space between letters	between letters affected	
Insert space between words	between words affected	
Reduce space between letters	between letters affected	
Reduce space between words	between words affected	