

# EARLY OSTEOLYSIS FOLLOWING SECOND-GENERATION METAL-ON-METAL HIP REPLACEMENT

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**Background:** Total hip arthroplasty with use of metal-on-metal bearings has been reintroduced as an alternative to the use of metal-on-polyethylene bearings because of theoretical advantages such as reduced wear and a lower prevalence of osteolysis. However, we observed early osteolysis in a cohort of patients who had been managed with second-generation metal-on-metal hip replacements and investigated the possible etiologic role of metal hypersensitivity.

**Methods:** We retrospectively analyzed 165 patients (169 hips) who had undergone primary cementless total hip replacement with a contemporary metal-on-metal total hip design between 2000 and 2002. After a minimum duration of follow-up of twenty-four months, nine patients (ten hips) had an osteolytic lesion localized to the greater trochanter. Skin-patch tests for hypersensitivity to metals were performed on the nine patients and on nine randomly selected patients with total hip replacements who did not have osteolytic changes and who were matched to the study cohort for age and gender. Microbiological cultures, histopathologic examinations, and immunohistochemical analysis were performed on samples of periprosthetic tissue that were collected during revision arthroplasty on two hips with early osteolysis.

**Results:** The patients with early osteolysis had a significantly higher rate of hypersensitivity reaction to cobalt compared with controls ( $p = 0.031$ ). The retrieved periprosthetic tissues showed no evidence of metallic staining, but histologic analysis revealed a perivascular accumulation of CD3-positive T-cells and CD68-positive macrophages and an absence of both particle-laden macrophages and polymorphonuclear cells. Immunohistochemical analysis demonstrated that bone-resorbing cytokines such as IL-1 $\beta$  and TNF- $\alpha$  were produced mainly by infiltrating lymphocytes and activated macrophages.

**Conclusions:** These findings raise the possibility that early osteolysis in patients with this second-generation metal-on-metal hip replacement is associated with abnormalities consistent with delayed-type hypersensitivity to metal. A prospective study in which a large group of patients is evaluated with multiple diagnostic methods is needed in order to establish whether there is a causal relationship between metal hypersensitivity and osteolysis.

**Level of Evidence:** Therapeutic Level III. See Instructions to Authors for a complete description of levels of evidence.

Early loosening of the first-generation metal-on-metal McKee-Farrar total hip prosthesis has been attributed to substandard implant design, inconsistent manufacturing tolerances, and poor surgical technique rather than suboptimal performance of the articulation<sup>1-3</sup>. In 1988, Muller and Weber reintroduced metal-on-metal bearings (Metasul; Sulzer Orthopedics, Winterthur, Switzerland) with improved materials, design, and manufacturing quality control as an alternative to the conventional metal-on-polyethylene articulation. Modern metal-on-metal hip prostheses have the theo-

retical advantage of producing less abrasive wear than metal-on-polyethylene prostheses do. In addition, the metal particles that are produced are smaller than polyethylene particles and, hence, they may induce less tissue reaction<sup>4-7</sup>.

Recent clinical studies on the outcomes associated with contemporary metal-on-metal total hip prostheses have shown mostly good results without osteolysis<sup>4,8,9</sup>, and total hip replacements involving these alternative bearings are being performed more frequently, particularly for younger patients. However, recent studies on patients with metal-on-metal bearings have shown that the serum levels of cobalt and chromium ions were significantly higher than those in normal individuals without implants<sup>10-12</sup>.

All metals that are in contact with biological systems



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corrode, and the released ions can activate the immune system by forming metal-protein complexes that are considered to be candidate antigens for eliciting hypersensitivity responses<sup>13-15</sup>. Although many studies have demonstrated the loosening of first-generation metal-on-metal hip prostheses in association with hypersensitivities to cobalt, nickel, and chromium<sup>16-18</sup>, it has not been determined whether the devices failed because the patients had a preexisting metal hypersensitivity or whether the patients became hypersensitive to metal as a result of the failed implants. Moreover, to the best of our knowledge, there have been only two studies that have suggested the possibility of metal hypersensitivity in patients with contemporary metal-on-metal hip replacements<sup>19,20</sup>.

In the present study, rapidly progressive osteolysis was observed in a cohort of patients with a second-generation metal-on-metal design. We investigated the possible role of metal hypersensitivity with skin-patch tests, histopathologic examinations, and immunohistochemical analysis of samples of periprosthetic tissue retrieved at the time of revision operations.

## Materials and Methods

### Patients

The present retrospective study was carried out under a protocol approved by the institutional review board at our medical center. Between April 2000 and March 2002, 258 patients (264 hips) underwent a primary cementless total hip replacement; all procedures were performed by a single surgeon (Y.-S.P.) through an anterolateral approach. Of these, 167 patients (171 hips) received a modern metal-on-metal bearing (DePuy/Johnson and Johnson, Leeds, United Kingdom) and ninety-one patients (ninety-three hips) received a ceramic-on-ceramic articulation (Lima-Lto, Udine, Italy). The decision to use the metal-on-metal bearing depended on the preference of the patient, who had been informed preoperatively of the specific benefits and risks associated with these two bearings. Of the 167 patients (171 hips) managed with a metal-on-metal prosthesis, two patients (two hips) were lost to follow-up before

a minimum of two years, leaving 165 patients (169 hips). The study group included eighty-six men (eighty-eight hips) and seventy-nine women (eighty-one hips) with a mean age of 54.8 years (range, twenty-one to eighty years) at the time of the operation. The average duration of follow-up was 27.2 months (range, twenty-four to forty-one months).

The diagnosis was osteonecrosis of the femoral head for ninety hips, osteoarthritis secondary to developmental dysplasia of the hip for twenty-one, osteoarthritis secondary to childhood septic arthritis for nineteen, posttraumatic osteoarthritis for twelve, primary osteoarthritis for eight, and miscellaneous diagnoses for nineteen.

All patients underwent metal-on-metal primary total hip arthroplasty with the S-ROM modular hip system (DePuy/Johnson and Johnson). This system consists of an Ultima cup made of Ti-6Al-4V alloy, an Ultima insert made of a cast cobalt-based Co-28Cr-6Mo alloy with a carbon content of >0.2% (high carbon), an S-ROM head made of a wrought cobalt-based Co-28Cr-6Mo alloy with a carbon content of <0.07% (low carbon), and an S-ROM stem made of Ti-6Al-4V alloy.

### Radiographic Review

Two independent observers (Y.-W.M. and S.-J.L.), who were not involved in the clinical care of the patients, examined the radiographs of each patient. Osteolysis was defined as a focal area of bone resorption, at least 2 mm wide, that was not evident on the immediate postoperative radiograph<sup>21</sup>. The immediate postoperative anteroposterior pelvic radiograph, the most current anteroposterior pelvic radiograph, and every other anteroposterior pelvic radiograph made between these two time-points were assessed for osteolysis.

### Clinical and Laboratory

#### Investigations for Infection

The nine patients (ten hips) who had an osteolytic lesion were evaluated with regard to risk factors for infection, such as a history of persistent drainage or delayed wound-healing. In addition, a physical examination of the hip was performed to

TABLE I Demographic Characteristics of Patch-Tested Patients

	Study Group	Control Group
Number of patients	9	9
Number of hips with osteolysis	10*	0
Male:female ratio	2:7	2:7
Age at index operation† (yr)	56.7 (41-68)	54.6 (44-65)
Diagnosis leading to hip arthroplasty		
Avascular necrosis	6	6
Secondary osteoarthritis	2	2
Primary osteoarthritis	1	0
Femoral neck fracture	0	1

\*One patient who had undergone bilateral total hip arthroplasty had symmetrical features of osteolysis in both hips. †The data are given as the median, with the range in parentheses.

detect any signs of inflammation, swelling, erythema, or localized tenderness. Laboratory investigations included a complete blood-cell count and measurement of the erythrocyte sedimentation rate and the C-reactive protein level.

#### *Skin-Patch Tests*

Skin-patch tests were performed according to the standard protocol of the International Contact Dermatitis Research Group for the nine patients with early osteolysis as well as for nine randomly selected patients from the series, matched for age and gender, who did not have an osteolytic lesion (Table I). Patients were tested for allergic reactions to nickel sulfate, cobalt chloride, and potassium dichromate (Chemotechnique Diagnostics, Tygelsjö, Sweden) with use of Finn Chambers (Epitest, Oy, Tuusula, Finland) on Scanpor Tape (Norgeplaster Aksjeselskap, Vennesia, Norway) that were applied to areas of the left side of the patient's upper back that were free of erythema and dermatitis. Patients returned forty-eight and ninety-six hours after application of the allergens for a reading of the patch test. The skin reactions were evaluated by a dermatologist (J.-M.Y.) who was blinded with respect to the clinical data, and the results were graded as 0 (negative reaction), + (erythema and edema), ++ (erythema and edema with papules and vesicles confined within the chamber), +++ (erythema and edema with papules and vesicles extending beyond the chamber), or IR (irritant reaction).

#### *Tissue Specimens*

Two of the nine patients who had osteolysis underwent a revision operation. One patient underwent revision surgery eighteen months postoperatively because of recurrent dislocation, and the other patient, who had well-fixed implants, required curettage and bone-grafting because of a large osteolytic lesion that was associated with a risk of fracture through the greater trochanter. Periprosthetic tissues were processed for analysis of formalin-fixed, paraffin-embedded sections as well as for multiple microbiological cultures. Histopathological analysis of hematoxylin and eosin-stained tissue samples was performed in order to determine general cellular features. The tissue sections also were viewed with polarized light, and the presence of metallic particles was determined according to the criteria of Willert et al.<sup>22</sup>.

#### *Immunohistochemical Analysis*

Four-micrometer-thick sections were placed onto coated slides, deparaffinized, subjected to a microwave oven treatment (10 mmol/L sodium citrate buffer [pH 6.5] for twenty minutes at 700 W), and immersed in Tris-buffered saline solution with 0.3% (volume per volume) hydrogen peroxide. After blocking with 1% (weight per volume) bovine serum albumin in Tris-buffered saline solution containing 0.05% (volume per volume) Tween 20 for thirty minutes, the slides were incubated for one hour at room temperature with monoclonal antibodies to B lymphocytes (CD20), T lymphocytes (CD3, CD4, CD8), and macrophages (CD68) for characterization of the cellular components. For detection of bone-resorbing cytokines, the slides

were incubated overnight at 4°C with a mouse anti-human interleukin-1 $\beta$  (IL-1 $\beta$ ) polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, California) at a dilution of 1:20 or a mouse anti-human tumor necrosis factor-alpha (TNF- $\alpha$ ) monoclonal antibody (HyCult Biotechnology, Uden, The Netherlands) at a dilution of 1:10. The immunoperoxidase staining was performed with use of the streptavidin-biotin peroxidase complex method (LSAB universal kit; Dako, Carpinteria, California). Equivalent amounts of the subtype-matched normal mouse IgG were used as negative controls, and tissue sections of tonsils were used as positive controls. The final reaction product was visualized with a liquid DAB substrate kit (Zymed Laboratories, San Francisco, California).

#### *Statistical Analysis*

To test for differences in the rate of metal hypersensitivity between patients with early osteolysis and the randomly selected age and gender-matched patients who did not have osteolytic lesions, McNemar tests were performed with use of standard software (SPSS for Windows, Version 11.5). The level of significance was set at  $p < 0.05$ .

#### **Results**

Periprosthetic osteolytic lesions were detected in nine patients (ten hips; 5.9%) with at least twenty-four months of follow-up. In nine of the ten hips with osteolysis, the osteolytic lesions were localized within the greater trochanter superior to the proximal-lateral aspect of the S-ROM sleeve (zone 1 according to the system of Gruen et al.<sup>23</sup>). The remaining hip had a large lesion that extended from the bone-prosthesis interface in zone 1 into the proximal aspect of the greater trochanter. The average size of the lesions was 132.5 mm<sup>2</sup> (range, 54.0 to 299.5 mm<sup>2</sup>). No osteolytic lesions were evident around the acetabular component. In all ten hips with periprosthetic osteolysis, the acetabular and femoral components were stable and well-fixed at the time of the latest follow-up evaluation. As no clear distinction could be made between the edge of the femoral head and the articulation surface of the acetabular component, wear could not be measured on plain radiographs.

There was no evidence of persistent drainage and no sign of inflammation in any of the ten hips. The complete blood-cell count, erythrocyte sedimentation rate, and C-reactive protein values were within normal limits in all nine patients. The gram stains, smears for acid-fast bacilli, and multiple microbiological cultures of all of the retrieved periprosthetic tissues from the two revised hips were negative.

Eight of the nine patients with early osteolysis, including the two patients who underwent revision surgery, had a positive patch test for cobalt chloride. In contrast, only two of the nine control patients had a positive test for cobalt chloride. Two patients in the study group and none of the patients in the control group had a positive test for nickel sulfate. One patient in the study group and two patients in the control group had a positive test for potassium dichromate (see Appendix). The patients with osteolysis had a significantly higher rate of

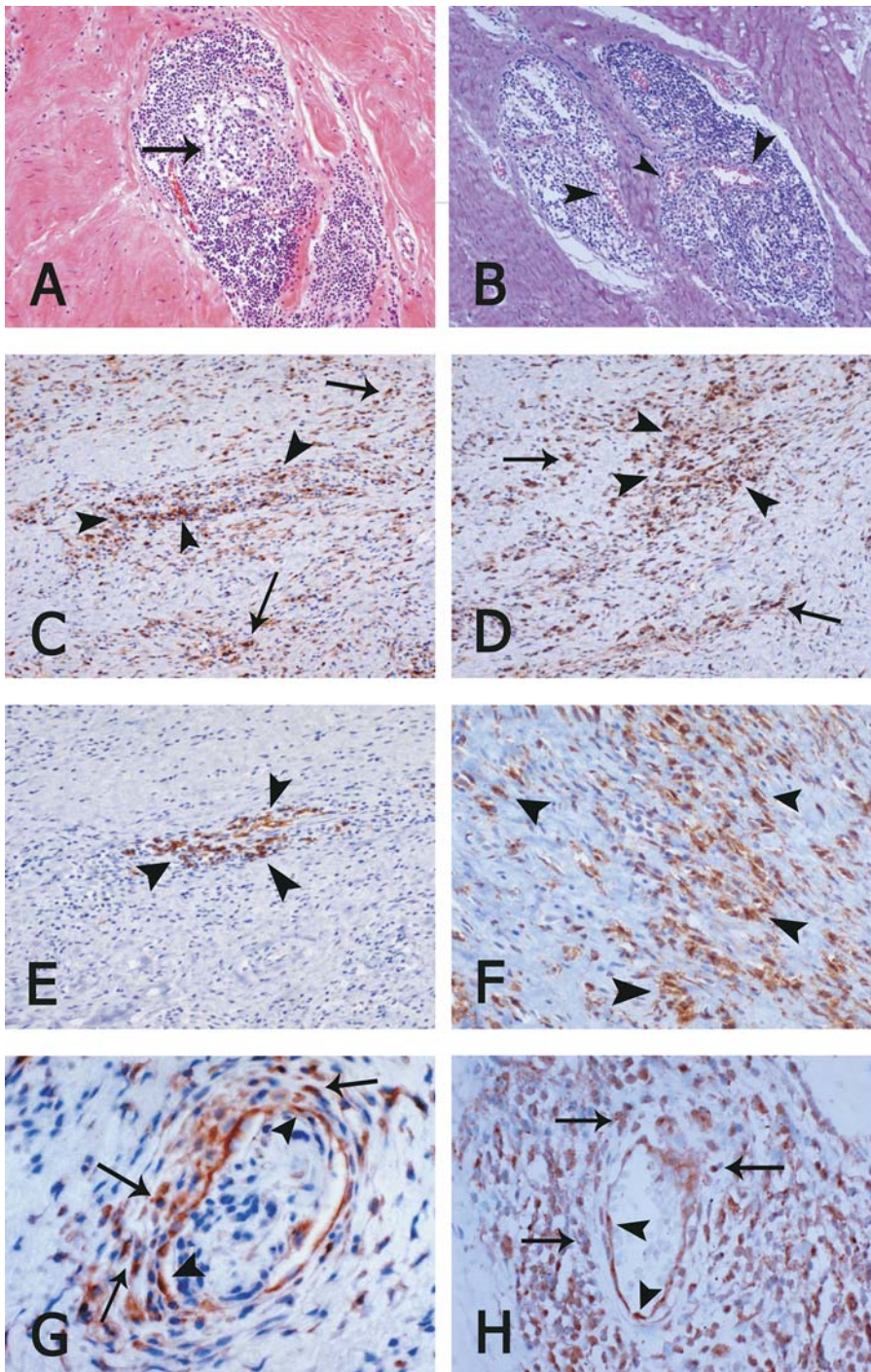


Fig. 1

A, Photomicrograph showing a lymphoid follicle in the periprosthetic tissue section and a germinal center as indicated by the arrow (hematoxylin and eosin; original magnification,  $\times 200$ ). B, The lymphocytic infiltrate was often prominent in perivascular areas (arrowheads on vessels) (hematoxylin and eosin; original magnification,  $\times 200$ ). C, CD4-positive T-cells (brown color) were seen around vessels (arrowheads) and throughout the tissue (arrows) (anti-CD4 immunostain; original magnification,  $\times 100$ ). D, CD8-positive T-cells (brown color) were also seen around vessels (arrowheads) and throughout the tissue (arrows) (anti-CD8 immunostain; original magnification,  $\times 100$ ). E, Staining for CD20 defined B-lymphocytic infiltrate (brown color, arrowheads) in perivascular areas (anti-CD20 immunostain; original magnification,  $\times 100$ ). F, Staining for CD68 defined diffusely infiltrated macrophages (brown color, arrowheads) throughout the tissue (anti-CD68 immunostain; original magnification,  $\times 200$ ). G, IL-1 $\beta$  was expressed in lymphocytes and macrophages (arrows) that often were located in perivascular areas in close proximity to vascular endothelial cells (arrowheads). Brown pigments detected by diaminobenzidine indicated the presence of IL-1 $\beta$  in the cytoplasm of the cells (anti-IL-1 $\beta$  immunostain; original magnification,  $\times 400$ ). H, TNF- $\alpha$  was also expressed in lymphocytes and macrophages (arrows) that often were located in perivascular areas in close proximity to vascular endothelial cells (arrowheads). Brown pigments detected by diaminobenzidine indicated the presence of TNF- $\alpha$  in the cytoplasm of the cells (anti-TNF- $\alpha$  immunostain; original magnification,  $\times 400$ ).

hypersensitivity reaction to cobalt chloride compared with controls ( $p = 0.031$ ), but, with the numbers available, there were no significant differences between the groups with regard to the rate of hypersensitivity reaction to nickel sulfate ( $p > 0.05$ ) or potassium dichromate ( $p > 0.05$ ).

Two patients who had a positive patch test for both cobalt chloride and nickel sulfate had had cutaneous symptoms. These patients had complained of a generalized eczematous

or urticarial reaction after the metal-on-metal prosthesis had been implanted.

The two hips that underwent revision surgery had no evidence of metallic staining in the periprosthetic tissue at the time of the revision, and no notch or groove was apparent in the neck of the femoral component that would have been suggestive of impingement between the socket and the femoral neck. The bearing surfaces of the prosthesis that was retrieved

because of recurrent dislocation were inspected with a non-contact, optical, three-dimensional scanner (REXCAN 400; Solutionix, Seoul, Korea). Although there were some fine scratches in the femoral head, there were no visible areas of wear when compared with unused prostheses.

Histologic examination of the retrieved periprosthetic tissues from the two revised hips showed perivascular infiltration of lymphocytes and mononuclear phagocytes in both cases. In one case, several lymphoid follicles also were noted. Neither particle-laden macrophages nor polymorphonuclear cells were seen on standard and polarized microscopic examination of the tissue sections. Immunophenotyping analysis revealed that most tissue-infiltrating lymphocytes in the periprosthetic tissue expressed the CD3 marker and therefore could be identified as T-cells. Additional staining showed that mixed CD4 and CD8-positive T-cells were present throughout the periprosthetic tissue. CD68-positive macrophages also were diffusely distributed throughout the periprosthetic tissue, and small numbers of CD20-positive cells were preferentially encountered within the lymphoid follicles. Immunohistochemical localization for the bone-resorbing cytokines revealed that IL-1 $\beta$  and TNF- $\alpha$  were expressed by T-cells and CD68-positive macrophages (Fig. 1).

### Complications

In addition to the two patients who required revision surgery, one patient required internal fixation of a periprosthetic fracture of the femur without revision of the femoral component. Another patient with high-riding developmental dysplasia of the hip had a nonunion following a subtrochanteric shortening derotational femoral osteotomy and cementless total hip arthroplasty. The nonunion was treated with dual onlay strut allografts and cable fixation. One patient had an incomplete sciatic nerve palsy, noted immediately after the index operation, that resolved almost completely by twelve months postoperatively.

### Discussion

Although reports on contemporary metal-on-metal hip prostheses have been generally favorable<sup>4,8,9</sup>, some retrieval studies have revealed evidence of metallic deposits in the periprosthetic tissues due to impingement of the neck on the socket<sup>24-26</sup>. In the cases of the two revised hips in the present study, no evidence of impingement of the components was seen at the time of revision surgery, no metallic deposits were detected in the periprosthetic tissues, and no metal particle-laden macrophages or foreign-body giant cells were found on standard and polarized microscopic examination of the tissue sections. We did, however, observe perivascular infiltrations of T-cells and macrophages in the tissue sections, which were similar to the histologic findings recently reported by Willert et al.<sup>20</sup>. Although the lack of observable metal debris under the polarized light microscope does not rule out the presence of undetectable metal wear particles in the nanometer size-range, our tissue findings are inconsistent with those typical of particle-induced osteolysis, which is associated with abundant particle-laden macrophages within periprosthetic

tissues<sup>27,28</sup>. Our findings also differ from those of Beaulé et al.<sup>29</sup>, who reported progressive diaphyseal osteolysis in patients with well-fixed, second-generation metal-on-metal hip replacements. We believe that the histologic features observed in the cases of our two patients are suggestive of an immune-system response to metal ions in the periprosthetic tissue. We speculate that antigen-specific sensitization of T-cells may play a role in the development of early osteolysis following second-generation metal-on-metal hip replacement.

Metal ions are allergens that are known to cause contact dermatitis, a delayed-type hypersensitivity reaction mediated by T-lymphocytes specific for the relevant metal<sup>13,14,30</sup>. Allergic reactions also can take place within the joint capsule and pericapsular tissue<sup>13</sup>. The most common metal sensitizer in humans is nickel, followed by cobalt and chromium, and cross-sensitivity reactions between metals are most common with nickel and cobalt<sup>14,15,30</sup>. The prevalence of metal sensitivity among patients with a well-functioning implant is roughly twice that in the general population and, among patients with a failed or poorly functioning implant, it is approximately six times that in the general population and approximately two or three times that among all patients with metal implants<sup>14</sup>. We found only one follow-up study that demonstrated an association between metal hypersensitivity and prosthetic failure in patients with second-generation metal-on-metal hip replacements<sup>19</sup>. The authors of that study analyzed 200 surface metal-on-metal hip replacements (containing nickel, cobalt, and chromium), including five replacements that failed because of aseptic or septic loosening. Three of the five hips that loosened were in patients who had positive skin-patch testing, all for nickel. In contrast, only three of eighteen controls had positive skin-patch tests. While that study documented a higher rate of metal hypersensitivity among patients with loose prostheses, it provided neither a statistical analysis of the results of the patch tests nor any histologic findings.

In the present study, the nine patients (ten hips) who had an osteolytic lesion had a significantly higher rate of hypersensitivity to cobalt, as determined with patch testing, compared with controls. These data agree with previous observations<sup>16-18</sup> that the loosening of first-generation metal-on-metal hip prostheses had an association with hypersensitivities to cobalt, nickel, and chromium. In one of the earliest studies investigating a possible association between metal hypersensitivity and aseptic loosening, Evans et al.<sup>18</sup> evaluated the histopathologic features of skin-biopsy specimens from four patients as well as skin biopsy specimens from one patient, in which they found a prominent granulomatous collection of cells with a surrounding zone of lymphocytes. Importantly, the author could not determine whether the patients became hypersensitive to metal because of the failed device or whether the device failed because the patients had a preexisting metal hypersensitivity.

Patch testing is the most common method used to diagnose contact allergy to metals<sup>31,32</sup>. However, it has certain limitations when used as a method to determine deep-tissue hypersensitivity. Patch testing involves exposure to the rele-

vant allergen for a short period of time (forty-eight to ninety-six hours), whereas a closed periprosthetic environment involves constant exposure to the orthopaedic implant<sup>14</sup>. While the antigen-presenting cells on dermal contact are dendritic cells, the possible antigen-presenting cells in a joint are synovial cells, which are capable of presenting metal ions to the pericapsular tissue-infiltrating T-lymphocytes<sup>13</sup>. In addition, immunologic tolerance can be induced by implantation of a metal prosthesis<sup>33,34</sup>, thus possibly diminishing the sensitivity of patch tests. Rooker and Wilkinson<sup>33</sup>, in a study in which fifty-four patients were given patch tests before and after metal-on-plastic hip replacement, reported that five of six patients had lost their metal sensitivity at the time of postoperative retesting.

Since Brown et al.<sup>35</sup> first used migration inhibition assays to investigate delayed-type hypersensitivity to metallic orthopaedic implants, only a few investigators<sup>36,37</sup> have applied in vitro delayed-type hypersensitivity testing methods to assess the biocompatibility of implanted devices. These methods remain a labor-intensive and clinically unpopular means of assessment. To date, a standardized, effective testing methodology for the clinical determination of hypersensitivity reaction to metal implants has not been well established.

Delayed-type hypersensitivity is characterized by antigen activation of sensitized T-cells releasing various cytokines that result in the recruitment and activation of macrophages<sup>38</sup>. Among the cytokines released by activated T-cells and macrophages, IL-1 $\beta$  and TNF- $\alpha$  potentially stimulate osteoclastogenesis<sup>39</sup>. In addition, TNF- $\alpha$  is also capable of downregulation of collagen-type-I synthesis in osteoblasts, another potentially important contributor to periprosthetic bone loss<sup>40</sup>.


Our immunohistochemical analysis of periprosthetic tissue from two hips with early osteolysis revealed that most tissue-infiltrating cells were CD3-positive T-cells and CD68-positive macrophages. It is notable that CD8-positive T-cells were also abundant in the periprosthetic tissue, suggesting that T-cell-mediated cytotoxicity might be associated with the development of osteolysis. We also identified the potent bone-resorbing cytokines such as IL-1 $\beta$  and TNF- $\alpha$  in the periprosthetic tissue in association with T-cells and activated macrophages.

Taken together, these findings raise the possibility that early osteolysis in patients with this second-generation metal-on-metal hip replacement is associated with a delayed-type hypersensitivity to metal, mainly cobalt. However, our data must be interpreted with caution because only two patients with early osteolysis had tissues available for histologic analysis. Additional weaknesses of our study include the lack of preoperative immunologic evaluation of the patients and the

limitation of skin-patch testing as a method of determining deep-tissue hypersensitivity. Additionally, we studied only one design of prosthesis and therefore cannot generalize our findings to all second-generation metal-on-metal hip prostheses.

It is unclear whether delayed-type hypersensitivity to metal contributed to the development of osteolysis or whether the patients became hypersensitive to metal secondary to an immune response to an osteolytic process. As a result of our findings, we are reluctant to implant modern metal-on-metal bearings in patients who have a history of allergic reaction to a metal implant or metallic wear. A prospective study in which a large group of patients with contemporary metal-on-metal bearings are evaluated with multiple testing methods, including in vitro delayed-type hypersensitivity assays as well as skin-patch testing, is needed to better explain any causal relationship between metal hypersensitivity and osteolysis.

### Appendix

 A table presenting the results of the patch tests is available with the electronic versions of this article, on our web site at [jbjs.org](http://jbjs.org) (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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