Immunologic Adverse Reaction Associated with Low-carbide Metal-on-metal Bearings in Total Hip Arthroplasty

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Abstract

Background An increased incidence of periprosthetic osteolysis, resulting in loss of biologic fixation, has been reported in contemporary THAs with low-carbide metal-on-metal compared with metal-on-polyethylene couple bearings. Although a hypersensitivity reaction attributable to Co and Cr debris is reportedly a potential cause for failure of THAs with high-carbide bearings, there are no evidence-based data for this reaction in low-carbide metal-on-metal bearings, although such hypersensitivity might be related to osteolysis.

Questions/purposes We investigated whether there were differences in immunologic hypersensitivity reactions in retrievals from revised THAs with ceramic-on-polyethylene versus metal-on-metal bearing couples.

Patients and Methods We compared newly formed capsule and periprosthetic interface membranes from revision surgery for aseptic failure from 20 patients with low-carbide bearings and 13 patients with ceramic-on-polyethylene

bearings. For control tissue, we obtained samples from the hip capsule during the primary THA implantation in 13 patients with low-carbide bearings and seven with ceramic-on-polyethylene bearings. We examined the tissues with conventional histologic and immunohistochemical methods.

Results Compared with tissue from the control subjects and patients with ceramic-on-polyethylene bearings, the tissues from patients with low-carbide metal-on-metal bearings were associated with (1) extensive necrosis and fibrin exudation in the newly formed hip capsule and (2) diffuse and perivascular lymphocytic infiltration of a higher degree than in the hips with ceramic-on-polyethylene bearings in conventional histologic examination, and (3) more T than B cells.

Conclusions The conventional histologic and immunohistochemical findings in tissues retrieved from failed THAs with low-carbide metal-on-metal bearings are consistent with a link between hypersensitivity and osteolysis with low-carbide bearing couples.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

Second-generation metal-on-metal (MOM) bearings (CoCr alloy) [31] were introduced in the 1990s to eliminate polyethylene wear-related osteolysis and subsequent aseptic loss of biologic fixation of these THAs. Most commercially used CoCr alloys are characterized on the basis of carbide content as high-carbide content ($> 0.2\%$ carbon) and low-carbide content ($< 0.07\%$ carbon)(by weight) [22].

Sikomet™ (Smith & Nephew Orthopaedics AG, Aarau, Switzerland) is a low-carbide, forged, vacuum-melted Co-28Cr-6Mo alloy with fine grain structure with an almost

carbide-free surface [14]. The volumetric wear rates of CoCr alloys are affected by the carbide content and the material combinations used, with the wear rate decreasing (pin-on-disc experiments) from a low-carbide head/low-carbide cup (5.6 ± 2.4 mg) to a low-carbide head/high-carbide cup (1.4 ± 0.9 mg) to a high-carbide head/high-carbide cup (1.3 ± 0.6 mg) [34]. The *in vivo* wear rate of Metasul® (Sulzer Medica, Winterthur, Switzerland) bearings (high-carbide head/high-carbide cup) showed a steady-state wear rate of 2 to 5 μ m per year [3, 30], whereas a higher wear rate of 7.6 μ m per year was reported for Sikomet™ (from a low-carbide head/low-carbide cup) bearing couples [29].

Some published studies have examined THAs with high-carbide bearings [5, 21, 36], but two clinical studies reported an apparently increased (3.75%–5.1%) aseptic loss of biologic fixation associated with focal and expansile osteolysis and a hypersensitivity reaction in patients who received low-carbide bearings [16, 22]. These authors [16, 22] suggested some characteristics of low-carbide bearings might be involved in the increased rate of periprosthetic osteolysis as no osteolysis has been associated with high-carbide bearings [5–7, 21] and because the only substantial difference between low- and high-carbide bearings is the carbon content in the bearing. Particle size and morphologic features are not affected by carbide content [8], which implies the increased wear rate of low-carbide and low-carbide/high-carbide combinations might be related to a higher number of particles released in the periprosthetic tissue, thus contributing to the development of osteolysis.

Increased metal serum levels occur in patients with high-carbide [2, 10, 11, 19] and low-carbide [20] bearings. As noted, patients with contemporary high-carbide bearings show a low incidence of osteolysis (at 33 months to 17 years) [4, 32, 39], although histologic evidence in retrievals suggests a delayed-type hypersensitivity (DTH) reaction to CoCr debris [36, 37]. DTH reactions are characterized by a strong cellular infiltrate, including neutrophils, macrophages, and T lymphocytes [17, 35]. Similar inflammatory infiltrates, including leukocytes, have been described around failed short-term cemented metal-on-polyethylene prostheses [1, 9].

Therefore we investigated whether there were differences in immunologic hypersensitivity reactions in retrievals from revised THAs with ceramic-on-polyethylene (COP) versus MOM bearing couples.

Patients and Methods

We retrospectively examined differences in conventional histology and immunocytochemistry of the pseudomembranes derived from revision surgeries performed between 1999 and 2006 in two age- and diagnosis-matched groups of patients (MOM, COP). For control tissue, we obtained samples from the hip capsules during 20 primary THAs (13 patients implanted with low-carbide bearings and seven implanted with COP bearings). We performed a post hoc power analysis using the modified Mirra grading system (Grades 1–3, Tables 1, 2) [4, 24, 37] to estimate the number of hips needed to have sufficient power for one grade difference between the two groups with an alpha of 0.5; this analysis suggested we would need 20 patients in each group. Initially, we had planned to include 20 hips for each experimental group and during the study period obtained 20 hips with MOM bearings but only 13 hips with COP bearings.

The patients of the COP group were operated on during the same period as patients in the MOM group. The MOM group included 20 patients (six men, 14 women), with a mean age $\pm$ SD of 62.5 ± 10 years (range, 42–80 years), who had consecutive revision surgeries at 4.6 ± 1.7 years (range, 3–7 years). The COP group included 13 patients (seven men, six women), with a mean age $\pm$ SD of 61 ± 9 years (range, 39–74 years), who had revision

Table 2. Grading of lymphocytic infiltration

Cells	Grade			
	–	1+	2+	3+
Lymphocytic infiltration	≤ 5 /HPF	6–20/HPF	21–50/HPF	> 50 /HPF

HPF = high-power field ($\times 400$).

Table 1. Grading of metal particles, giant cells, and neutrophils*

Particles/cells	Grade		
	1+	2+	3+
Metal particles	Slate blue histiocytes	Dusty black histiocytes	Jet black histiocytes
Giant cells	≤ 1 /HPF	2–4/HPF	≥ 5 /HPF
Neutrophils	≤ 5 /HPF	6–49/HPF	≥ 50 /HPF

* Modified Mirra classification [4, 24, 37]; HPF = high-power field ($\times 400$).

surgeries at 4.8 ± 3.4 years (range, 1–13 years). The indications for primary THA in both groups were primary osteoarthritis or secondary osteoarthritis from developmental dysplasia of the hip. All primary THAs were performed from 1996 to 2002 and all were unilateral. MOM bearings were selected for biologically young and active patients (active community walkers according to the classification of Perry et al. [28]) or overweight patients (body mass index > 30). We considered a history of rheumatoid diseases (eg, rheumatoid arthritis) as a contraindication for use of MOM bearings because of the autoimmune nature of this disease, and thus we did not implant prostheses with MOM bearings in these patients. A 22-mm metal ball head on a polyethylene cup was implanted in seven patients with highly dysplastic and highly dislocated hips and 17 cemented UHMPE cups were implanted in 17 osteoporotic acetabula. All patients had subsequent revision surgery for aseptic loss of biologic fixation associated with focal osteolysis. The age of patients and time between the primary and revision surgeries were similar in the MOM and COP groups ($p = 0.68$ and 0.8 , respectively).

We obtained erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in all patients of both groups preoperatively to the last evaluation, whereas tissue specimens from the revision surgeries and primary joint capsules routinely underwent three to four cultures for each patient. Microscopic examination of intraoperatively obtained synovial fluid including leukocyte count percent and Gram stains were done for all patients who underwent revision surgeries where fluid was intraoperatively evident. To rule out the diagnosis of infection at the site of a revised THA, two or more of the following criteria were required: (1) a positive intraoperative culture; (2) synovial fluid cell count greater than 4200 with more than 80% polymorphonuclear cells for the differential count; and (3) final histologic evidence (formation of microabscesses, including great aggregates of neutrophils). Elevated ESR and CRP, as nonspecific tests, were used in conjunction with a careful history and physical examination [30].

All patients had a unilateral primary arthroplasty and all had the same cementless third-generation Zweymüller-Plus[®] prosthesis (Smith & Nephew Orthopaedics AG) implanted. The Zweymüller-Plus[®] system includes the rectangular SL-Plus[®] stem and the Bicon[®] threaded titanium cup that was assembled with either MOM or COP articulations. A RCH-1000 Chirulen[®] UHMWPE liner was interposed between the Bicon[®] shell and the Sikomet[™] SM21 Co28Cr6Mo low-carbon alloy articulating surface (ASTM F799 and 1537, ISO 5832-12). A 28-mm-diameter metal femoral head manufactured from Sikomet[™] SM21 was used in all patients with MOM articulation. The 28-mm ceramic femoral head implanted in the hips of

patients in the COP group was made from alumina (Ceramtec, Plochingen, Germany). The polyethylene articulating inlay was machined from barstock UHMWPE molded forms (ISO 5834-2:2006). We received institutional review board approval for this study.

The indication for revision in the MOM and COP groups was aseptic radiographic loosening [11] of the stem, cup, or both, with focal and/or expansile osteolysis associated with pain and disability. We defined radiographic failure of the cup as a rotational change of alignment greater than 3° in relation to the biischial line on the AP radiograph, continuous osteolysis greater than 2 mm in at least two De Lee and Charnley zones, or axial migration of the cup of 3 mm or greater [11]. Definite radiographic loosening of the stem was defined as axial subsidence greater than 2 mm in relation to the tip of the greater trochanter, new varus inclination of the stem greater than 3° , continuous periprosthetic osteolysis greater than 2 mm in two or more adjacent Gruen zones, and/or continuous radiolucent lines greater than 2 mm in thickness in more than two Gruen zones [11].

We had tissue samples from all 33 patients of the two experimental groups (MOM, COP) from their revision arthroplasties (membranes from the acetabular and femoral interfaces and capsules), and from the 20 patients of the control group from their primary THAs (13 patients with MOM implants and seven with COP implants). The tissue samples were fixed in 10% neutral-buffered formalin and examined by light microscopy using conventional histologic and immunocytochemical techniques.

Conventional histologic techniques included tissue sections stained with hematoxylin and eosin, periodic acid Schiff, van Gieson's, and Pearl's stain. Four to eight sections were examined from each patient. The amount of metal (CoCr) debris containing macrophages, the number of giant cells, and the neutrophilic infiltration were estimated and graded according to the modified Mirra classification [4, 24, 37] (Tables 1, 2). Lymphocytic infiltration was graded by counting perivascular and diffuse infiltrating lymphocytes per high-power field (HPF) ($\times 400$) (Table 2). Three independent pathologists (MR, PA, VB), who were blinded to the source of the specimens (MOM or COP group), examined 20 randomly selected histologic specimens including four sections each to test variability of grading. They graded lymphocytes according to the modified Mirra classification (Grades 1–3). A kappa value for interobserver agreement was 0.91.

Immunocytochemical analysis of formalin-fixed paraffin-embedded tissue sections was conducted using the ChemMate[™] Dako EnVision[™] Detection System, horse radish peroxidase (HRP)/diaminobenzidine (DAB), rabbit/mouse antibody (DAKO, Glostrup, Denmark) in a DAKO autostainer as described previously [26], and included

Table 3. Antibodies used in immunohistochemical evaluation of tissue samples

Antibody	Marker	Source
CD20	B lymphocytes	Biogenex, San Ramon, CA
CD3	T lymphocytes	Novocastra, Newcastle upon Tyne, UK
CD4	T helper cells	Labvision, Fremont, CA
CD8	T suppressor cells	DAKO, Glostrup, Denmark
CD138	Plasma cells	Novocastra, Newcastle upon Tyne, UK
CD57	Natural killer cells	DAKO, Glostrup, Denmark
CD68 (PGM1)	Histiocytes	Labvision, Fremont, CA
CD1 α	Langerhans' cells	Novocastra, Newcastle upon Tyne, UK

markers of T and B lymphocytes, T suppressor and T helper cells, plasma cells, natural killer (NK) cells, macrophages, and Langerhans' cells. Appropriate positive and negative controls were used for each antibody (Table 3). Paraffin-embedded tissue sections (4 μ m thick) were deparaffinized and rehydrated. Where necessary, for some of the antibodies, tissue sections were subjected to heat-induced epitope antigen retrieval using an electric pressure cooker and Trilogy™ (Cell Marque, Hot Springs, AR). Three of us (MR, PA, VB) scored the degree of immunoreactivity for all antibodies semiquantitatively, taking into account the percentage of positive cells: weak (1+), moderate (2+), and strong (3+) for less than 5%, 6% to 49%, and greater than 50% positive cells, respectively, showing a kappa value of 0.87 [15, 17, 35].

We did not use any qualitative or quantitative measures for Co or Cr metal debris. No specific study (eg, scanning electron microscopic analysis) was performed in the retrieved bearing couples.

A skin patch test containing CoCr alloy, provided by the manufacturer, was performed postoperatively in all patients of the MOM group. However, there was an inconsistency regarding previous contacts with Cr and Co ions (dental work, necklaces, etc) among the patients of the MOM group. Only one patient (5%) had hypersensitivity to the skin patch test.

ESR and CRP were within normal limits and cultures of intraoperatively obtained tissue specimens were negative for bacteria.

Differences in the number of metal particles, neutrophilic infiltration, and CD68+ macrophages between independent groups (MOM versus COP) were evaluated with the Mann-Whitney U test. Differences between related groups (primary hip capsules versus periprosthetic tissues of the same group) were tested with the Wilcoxon sign test. Statistical analysis was performed with SPSS® (Version 12 for Windows®; SPSS Inc, Chicago, IL).

Fig. 1 Extensive necrosis is seen in the synovial membrane in association with Grade 3+ lymphocytic infiltration of the neocapsule from a revised THA with MOM bearings (Stain, hematoxylin and eosin; original magnification, $\times$ 200).

Results

The conventional histologic study showed (1) extensive necrosis in 90% of hips with MOM bearings but none in the hips in the COP group or in control tissues (Fig. 1; Table 4); (2) fibrin exudation in the newly formed hip capsule in 10% of hips with MOM bearings but none in the other hips; and (3) a higher degree ($p < 0.001$) of diffuse and perivascular lymphocytic infiltration in hips with MOM bearings than in the hips with COP bearings (Fig. 2; Table 4).

The immunohistochemical methods suggested more T cells than B cells (Fig. 3), particularly CD8 + (suppressor) (Fig. 4) in periprosthetic tissues of hips with MOM bearings (Table 4).

Discussion

Two studies [16, 22] have reported an increased incidence of periprosthetic osteolysis in contemporary THAs with low-carbide MOM bearing couples. Although a hypersensitivity reaction attributable to Co and Cr debris has been suggested [5, 7, 21] as a potential cause for failure of THAs with high-carbide bearings, there are no evidence-based data for this reaction in low-carbide MOM bearings. Therefore we investigated whether there were differences in immunologic hypersensitivity reactions in retrievals from revised THAs with COP versus MOM bearing couples.

The limitations of our study include the following. First, the retrospective nature of this study resulted in a lack of all specimens derived from primary surgeries although we

Table 4. Histologic and immunocytochemical findings in MOM and COP revision and control groups

Particles/cells	MOM revision	COP revision	MOM control	COP control	p Value*	MOM vs COP revision		MOM revision vs control		COP revision vs control	
						MOM	vs COP	MOM	revision	COP	revision
Metal particles [†]											
1+	5/20 (25%)	5/13 (38.5%)	0/13 (0%)	0/7 (0%)	> 0.05						
2+	12/20 (60%)	6/13 (46.2%)	0/13 (0%)	0/7 (0%)							
3+	3/20 (15%)	2/13 (15.4%)	0/13 (0%)	0/7 (0%)							
Mean ± SD	1.90 ± 0.641	1.77 ± 0.72	0 ± 0	0 ± 0							
Giant cells [†]											
1+	20/20 (100%)	7/13 (53.8%)	0/13 (0%)	0/7 (0%)	0.001						
2+	0/20 (0%)	2/13 (15.4%)	0/13 (0%)	0/7 (0%)							
3+	0/20 (0%)	4/13 (30.8%)	0/13 (0%)	0/7 (0%)							
Mean ± SD	1 ± 0	1.77 ± 0.93	0 ± 0	0 ± 0							
Neutrophils [†]											
1+	12/20 (60%)	12/13 (92.3%)	13/13 (100%)	7/7 (100%)	> 0.05			0.023			> 0.05
2+	5/20 (25%)	1/13 (7.7%)	0/13 (0%)	0/7 (0%)							
3+	3/20 (15%)	0/13 (0%)	0/13 (0%)	0/7 (0%)							
Mean ± SD	1.55 ± 0.76	1.08 ± 0.28	1 ± 0	1 ± 0							
Lymphocytic infiltration [‡]											
0	0/20 (0%)	3/13 (23.1%)	6/13 (46.2%)	4/7 (57.1%)	< 0.001			0.013			> 0.05
1	4/20 (20%)	8/13 (61.5%)	6/13 (46.2%)	3/7 (42.9%)							
2	4/20 (20%)	2/13 (15.4%)	0/13 (0%)	0/7 (0%)							
3	12/20 (60%)	0/13 (0%)	1/13 (7.7%)	0/7 (0%)							
Mean ± SD	2.40 ± 0.82	0.92 ± 0.64	0.69 ± 0.85	0.43 ± 0.53							
CD68+ macrophages [‡]											
1	2/20 (10%)	1/13 (7.7%)	9/13 (69.2%)	7/7 (100%)	> 0.05			0.008			0.001
2	4/20 (20%)	5/13 (38.5%)	4/13 (30.8%)	0/7 (0%)							
3	14/20 (70%)	7/13 (53.8%)	0/13 (0%)	0/7 (0%)							
Mean ± SD	2.60 ± 0.68	2.46 ± 0.66	1.3 ± 0.48	1 ± 0							
Necrosis											
Yes	18/20 (90%)	0/13 (0%)	0/13 (0%)	0/7 (0%)							
No	2/20 (10%)	13/13 (100%)	13/13 (100%)	7/7 (100%)							
Fibrin exudation											
Yes	2/20 (10%)	0/13 (0%)	0/13 (0%)	0/7 (0%)							
No	18/20 (90%)	13/13 (100%)	13/13 (100%)	7/7 (100%)							

Table 4. continued

Particles/cells	MOM revision	COP revision	MOM control	COP control	p Value*	MOM vs COP revision		MOM revision vs control		COP revision vs control	
T cells/B cells ratio (CD3+/CD20+)											
T cells > B cells	13/20 (65%)	12/13 (92%) [§]	6/13 (46%)	4/7 (57%)							
B cells > T cells	7/20 (35%)	1/13 (8%) [§]	7/13 (54%)	3/7 (43%)							

* Wilcoxon sign or Mann-Whitney test; † scoring was performed according to modified Mirra classification [4, 24, 37]; ‡ scoring was performed as described in Patients and Methods; § attributable to extremely sparse lymphocytic infiltration observed in COP retrievals, statistical analysis for T and B cells between COP and MOM groups would be impossible; MOM = metal-on-metal THA; COP = ceramic-on-polyethylene THA.

Fig. 2 Grade 3+ diffuse and perivascular lymphocytic infiltration of the neocapsule from a revised THA with MOM bearings is shown (Stain, hematoxylin and eosin; original magnification, ×400).

Fig. 3A–B There was an excess of (A) T lymphocytes (CD3+) over (B) B lymphocytes (CD20+) at the acetabulum-cup interface seen with this revised THA with MOM bearings (Stain, EnVision™, HRP/DAB; original magnification, ×400).

had all specimens from the revision surgeries. Second, the power of the study was relatively weak because of the small sample. Third, there was inconsistency in the history

Fig. 4A–B (A) T suppressor (CD8+) and (B) T helper (CD4+) lymphocytes at the neocapsule from a revised THA with MOM bearings are shown (Stain, EnVision™, HRP/DAB; original magnification, $\times 400$).

of previous contact with CoCr and lack of skin patch testing before primary implantation. However, most characteristic histologic and immunohistochemical findings indicative of DTH were present in the hips with MOM bearings almost exclusively. Fourth, in our patients with MOM bearings, we had no definitive information regarding previous contacts with Cr and Co ions (dental bridges, osteosynthesis material containing Co and Cr, etc), and we did not investigate any genetic predisposition for sensitivity to Co and Cr. However, we presumed the first sensitization of T lymphocytes was derived from continuous contact with released metal debris from the CoCr bearings after prosthesis implantation [38].

The histologic findings in the tissues retrieved from hips with MOM bearings differentiate them from the hips with COP bearings: extensive necrosis solely in nearly all hips with MOM bearings, fibrin exudation in the newly formed hip capsule, and a higher degree of diffuse and perivascular lymphocytic infiltration. These findings are consistent with

the hypothesis that one of the causes of periprosthetic osteolysis and loss of biologic fixation of a THA with implantation of a prosthesis with MOM bearings could be a hypersensitivity reaction [22, 23, 38]. Extensive fibrin exudation was reported in a similar study [22]. Necrosis [2, 18, 22, 37, 39] in the newly formed hip capsule was observed in studies of Metasul® bearings [36–39], whereas it was not a permanent feature in a study of Sikomet™ bearings [22]. The increased lymphocytic infiltration in hips with MOM bearings compared with COP bearings that we observed is consistent with a report of Sikomet™ bearings [22].

A previous report [27] described perivascular accumulation of CD3+ T cells and CD68+ macrophages in periprosthetic tissues collected during revision of THAs with MOM bearings with high-carbide content. CD4+ and CD8+ T cells can mediate DTH [12, 13, 25, 33]. In our study, the increased incidence of T lymphocytes (CD3+/CD20+) over B lymphocytes in the periprosthetic retrievals in THAs with MOM bearings could be considered consistent with a DTH reaction.

Our histologic and immunohistochemical findings support the hypothesis that one of the major causes of periprosthetic osteolysis and loss of biologic fixation of THAs using the contemporary Zweymüller-Plus® prosthesis with low-carbide bearings could be a hypersensitivity reaction to CoCr alloy.

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