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Exhibit Selection

Understanding Why Metal-on-Metal Hip Arthroplasties Fail

A Comparison Between Patients with Well-Functioning and Revised Birmingham Hip Resurfacing Arthroplasties

AAOS Exhibit Selection

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Background: A large proportion of metal-on-metal hip arthroplasty failures are due to unexplained pain. The mechanism of failure has been thought to be associated with factors that increase material loss, including specific design features and surgical positioning of components. However, recent evidence suggests that there is not a simple dose-response relationship. An analysis of failed metal-on-metal hip arthroplasties involving a single design was performed in an attempt to help resolve this issue. Our aim was to identify the clinical and component variables associated with failure of metal-on-metal hip arthroplasties, particularly in patients undergoing revision arthroplasty because of unexplained hip pain, and to clarify the role of material loss.

Methods: We prospectively recruited fifty-five patients who were undergoing revision of a metal-on-metal Birmingham Hip Resurfacing System (BHR) arthroplasty (Smith & Nephew). We collected clinical data preoperatively, intraoperatively, and following the revision arthroplasty. Data included chromium and cobalt levels in whole blood, which were measured with use of inductively coupled plasma mass spectrometry (ICPMS), and component orientation, which was typically measured with use of computed tomography (CT) scans. The wear of the retrieved components was also quantified postoperatively. All parameters were compared with those in a comparable group of patients with a well-functioning BHR arthroplasty.

Results: Sixty-nine percent of the patients who underwent revision arthroplasty did so following a diagnosis of unexplained hip pain. When compared with patients with a well-functioning arthroplasty, patients who underwent revision arthroplasty had a significantly higher acetabular cup inclination angle ($p < 0.01$), a significantly smaller femoral head diameter ($p < 0.01$), and significantly higher blood cobalt and chromium ion levels ($p < 0.01$). However, almost 50% of the patients who underwent revision arthroplasty had blood metal ion levels below the clinical threshold of 7 ppb and low component wear rates of <5 μm/year.

Conclusions: In a large number of patients with unexplained hip pain leading to revision of a metal-on-metal hip arthroplasty, the acetabular cup orientation was satisfactory and the material loss rate was low. We suspect that patient-specific factors may have been responsible for the failure in a large proportion of these patients.

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TABLE I Comparison of Revised and Well-Functioning Metal-on-Metal Arthroplasties

	Revised	Well-Functioning	P Value
No. of patients	55	42	
Sex *(female:male)*	36:19	21:21	0.15
Time since initial arthroplasty* *(mo)*	45.0 (12.0 to 121.0)	42.0 (24.0 to 60.0)	0.13
Age at index arthroplasty* *(yr)*	55.0 (16.0 to 71.0)	59.0 (40.0 to 75.0)	0.09
Blood cobalt level before revision* *(ppb)*	7.5 (0.9 to 167.0)	2.3 (0.8 to 170.0)	<0.01
Blood chromium level before revision* *(ppb)*	5.6 (0.4 to 183.0)	2.4 (0.2 to 180.0)	<0.01
Head diameter* *(mm)*	46.0 (38.0 to 54.0)	50 (42.0 to 58.0)	<0.01
Cup inclination angle* *(deg)*	50.0 (24.0 to 73.0)	42 (12.0 to 60.0)	<0.01
Cup version angle* *(deg)*	17 (–34.0 to 45.0)	14.5 (–20.0 to 53.0)	0.84
Cup wear rate* *(μm/yr)*	6.2 (0.3 to 153.8)	—	—
Head wear rate* *(μm/yr)*	5.4 (0.0 to 52.4)	—	—
Oxford Hip Score*	—	14.0 (12.0 to 28.0)	—

*The values are given as the median, with the range in parentheses.

Despite the clinical advantages of metal-on-metal hip resurfacing and total hip arthroplasty with use of large-diameter femoral heads, joint registries have reported higher than expected failure rates for both of these alternatives to conventional hip replacement[1], with an unusually high prevalence of failure because of unexplained pain[2]. These data have also shown a significant variation among the failure rates of different metal-on-metal hip prosthesis designs[1]; the reported five-year failure rate ranged from 4.3% for the best-performing design, the Birmingham Hip Resurfacing System (BHR; Smith & Nephew, Memphis, Tennessee), to 12% for the worst-performing design, the Articular Surface Replacement (ASR; DePuy Orthopaedics, Warsaw, Indiana)[1].

It has been speculated that adverse soft-tissue reactions are responsible for a large proportion of metal-on-metal hip arthroplasty revisions performed because of unexplained hip pain, and studies have shown these revisions to be associated with increased material loss, in the form of high component wear[3] and/or elevated metal ion levels in the blood[4,5], occurring as a result of reduced coverage of the femoral head[6,7]. The extent of femoral head coverage is influenced by surgical, patient, and implant-specific factors, primarily the implantation of the acetabular cup with an excessive inclination angle[6-10] and the implantation of components that have reduced femoral head diameter[9,10], articular arc[6,9,11], and head-cup clearance[11]. In the worst-case scenario, reduced coverage of the femoral head may result in edge-loading and increased wear of the bearing surfaces[8,12]. In addition, recent evidence has suggested that failure of metal-on-metal hip arthroplasties because of unexplained hip pain can also occur secondary to metal loss from sources other than the bearing surface, such as corrosion and mechanical wear at the head-neck junction of a large-diameter metal-on-metal femoral component[13-15]. Thus, the unifying hypothesis in the literature regarding unexplained hip pain

TABLE II Criteria Used for Diagnosing the Reason for Revision of a Metal-on-Metal Hip Arthroplasty

	Diagnostic Criteria*
Unexplained hip pain	Absence of intraoperative loosening of components, infection (see below), gross malalignment (see below), component size mismatch, and fracture (on imaging and seen intraoperatively)
Aseptic acetabular loosening	Diagnosed intraoperatively (preoperative imaging has a high false-negative rate)
Aseptic femoral loosening	Diagnosed intraoperatively (preoperative imaging has a high false-negative rate)
Infection	Positive if postoperative cultures are positive for infection. Negative if preoperative CRP is <10 mg/L or if preoperative CRP is >10 mg/L but postoperative cultures are negative for infection
Dislocation	Patient-reported (with or without radiographic evidence)
Periprosthetic fracture	Radiographic evidence
Misalignment	Imaging (CT or radiography) shows cup inclination of >70° and/or cup version associated with impingement
Component mismatch	Postoperative assessment of components

*CRP = C-reactive protein, and CT = computed tomography.

leading to failure of a metal-on-metal hip arthroplasty has involved an adverse soft-tissue reaction to metal wear debris (implant material loss).

However, the role of acetabular cup orientation is much less certain following a recent study that showed many failed hip arthroplasties to have a satisfactory cup inclination angle[14]; although the cup version angle may play a role in these cases, it appears to contribute much less to the component wear rate than the inclination angle does[16]. The role of material loss is also uncertain, given that the majority of the patients in the study who had failed metal-on-metal hip arthroplasties had acceptable blood metal ion levels prior to revision and components that showed low wear at retrieval[12].

It is clear that we require a better understanding of the failure mechanisms of the current generation of metal-on-metal hip arthroplasty implants, particularly the role of surgical, implant, and patient-specific factors. This is essential to improve the outcome of metal-on-metal hip arthroplasties and to aid in the management of the estimated 1 million patients who have received a metal-on-metal hip implant over the past two decades.

The present study compared a consecutive group of patients who had undergone revision of a BHR hip arthroplasty with a group of patients with a "well-functioning" BHR arthroplasty. This study of a single implant design was designed to test three hypotheses: (1) revision of a metal-on-metal hip resurfacing is most commonly due to unexplained hip pain; (2) unexplained hip pain is associated with malpositioning of the acetabular component; and (3) unexplained hip pain occurs secondary to elevated blood metal ion levels.

Materials and Methods

We performed a retrospective study of prospectively collected data comparing two groups totaling ninety-seven patients. Fifty-five patients had undergone revision of a failed metal-on-metal BHR arthroplasty, and forty-two patients in the comparison group had a well-functioning BHR hip arthroplasty (Table I).

Failed Metal-on-Metal Hip Arthroplasties

The fifty-five patients in the revision group corresponded to a consecutive series of BHR arthroplasty implants sent to our implant retrieval laboratory between February 2008 and September 2010. The laboratory operates with the approval of the Human Tissue Authority and the local institutional ethical committee, and it has received implants from ninety-three referring surgeons working in fifty-six hospitals throughout the United Kingdom. Our methods of operation and our patient consent form were available to the public on our university web page. This web page enabled surgeons to contact us prior to removal of the hip implants and maximized our ability to obtain prospective data, including metal ion levels in the blood prior to revision and intraoperative findings. Thus, the referring surgeon contacts our laboratory prior to the majority of the revision

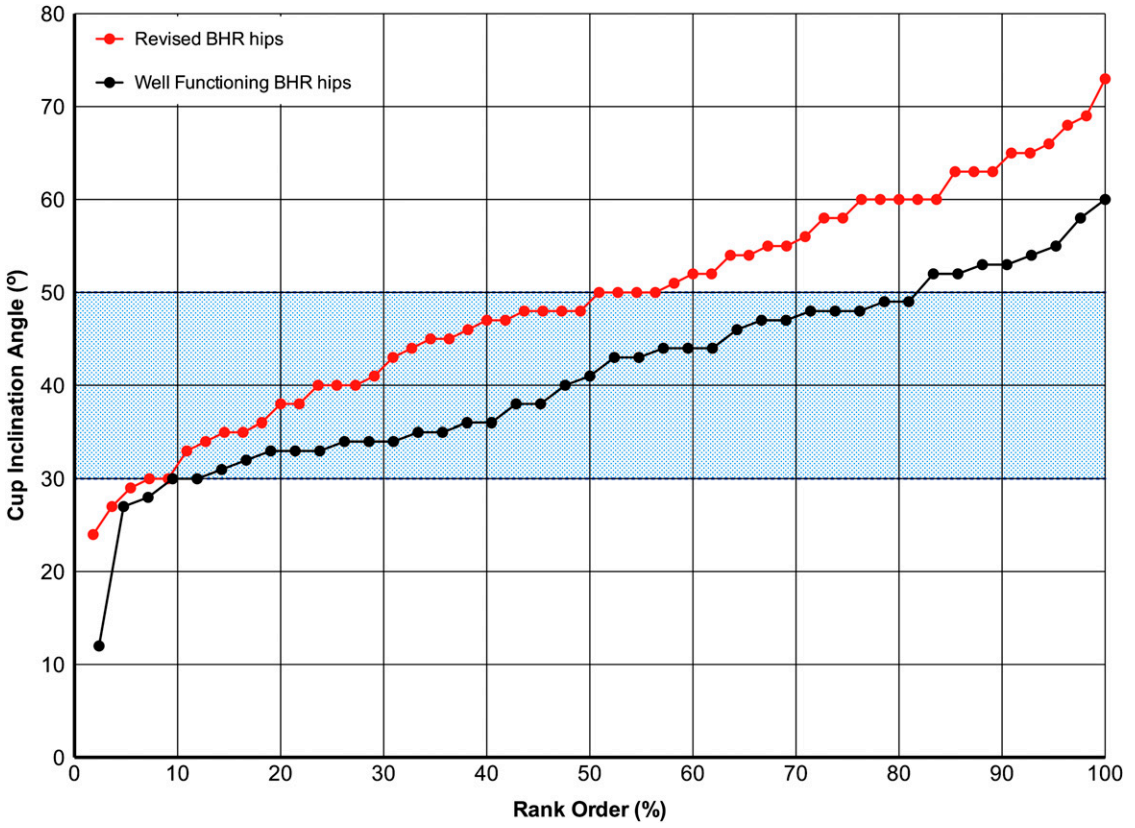

Fig. 1

Graph showing the rank order (expressed as a percentage) of each patient according to acetabular cup inclination angle. The shaded area indicates the "safe zone" for cup inclination described by Lewinnek et al.[20]. In the revision group, 51% of hips were implanted within this zone.

arthroplasties from which we receive implants. We recorded potentially relevant clinical and component variables relevant to failure and material loss for each patient in the study group (Table I).

Inclusion criteria for both groups included unilateral arthroplasty involving a large-diameter (>36-mm) BHR femoral head and a one-piece BHR acetabular cup. Since the study focused on material loss, patients were excluded if the prosthesis was revised less than twelve months after the primary arthroplasty (in order to exclude any confounding effect of "bedding-in" wear, which typically occurs in the first twelve months after implantation[17,18]). Additionally, patient data were required to be sufficiently complete to diagnose the reason for revision according to the categories used by the National Joint Registry of England and Wales[2].

Well-Functioning Metal-on-Metal Hip Arthroplasties

We recruited a group of forty-two patients who attended our clinic for routine follow-up of a unilateral BHR arthroplasty. These patients were asymptomatic and reported no problems with the hip arthroplasty. Each patient underwent clinical assessment involving measurement of cobalt and chromium levels in whole blood, hip function assessment with use of the Oxford Hip Score, and radiography or computed tomography (CT) scanning. Again, factors relevant to clinical failure and material loss were recorded (Table I).

Diagnosis of the Reason for Revision

The reason for revision was diagnosed according to the categories used by the National Joint Registry of England and Wales[2], which were infection, aseptic acetabular loosening, aseptic femoral loosening, fracture, dislocation, component mismatch, misalignment, and unexplained hip pain (Table II). The minimum data set for patients who underwent revision arthroplasty consisted of preoperative hip radiographs and serum C-reactive protein (CRP) level, intraoperative findings regarding component fixation, and postoperative microbiological cultures. Patients who underwent revision arthroplasty were excluded if they did not have the minimum required clinical data set.

The diagnosis of unexplained pain was determined by the absence of infection, loosening, impingement, dislocation, or subluxation, plus the presence of pain originating in the hip. Pain was diagnosed as originating in the hip after exclusion of spinal and other non-hip sources of pain by an experienced orthopaedic surgeon, and this diagnosis was often supported by diagnostic injection of local anesthetic into the hip joint and/or resolution of the pain after revision arthroplasty.

Measurement of Cup Orientation

Acetabular cup orientation was measured on either CT scans or radiographs. If CT scans were not available, acetabular version was measured only if both anteroposterior and lateral radiographs were available. CT scans were made with use of 0.75-mm collimation (high resolution) and artifact minimization software (involving 16-bit data processed on an extended scale), both of which enabled visualization of the detail required to separate the metallic cup face from the metallic large-diameter femoral head. The radiation dose was 1.7 mSv, which is much lower than the 10 mSv resulting from a traditional pelvic CT scan. Acetabular inclination and version angles were measured with use of a validated three-dimensional CT reconstruction software package[19].

Analysis of Blood Cobalt and Chromium Levels

All patients underwent analysis of cobalt and chromium levels in whole blood obtained from the antecubital vein with use of a 21-gauge needle

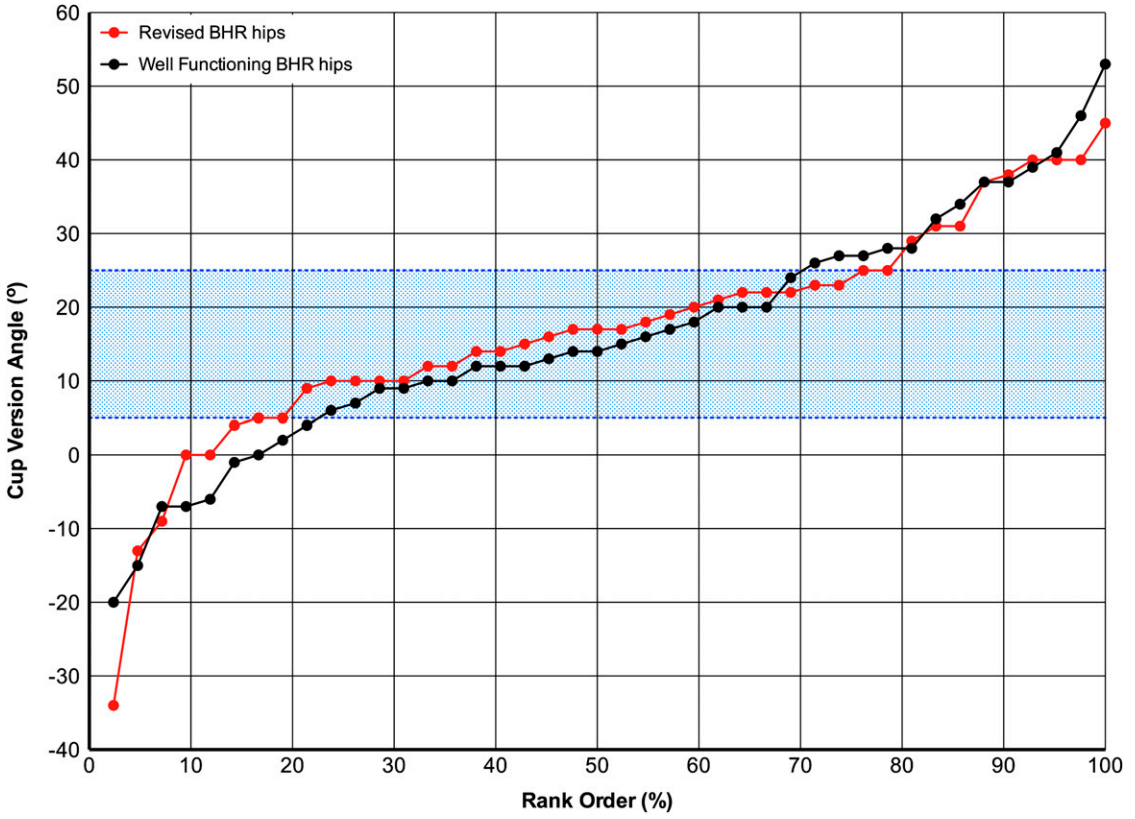

Fig. 2

Graph showing the rank order (expressed as a percentage) of each patient according to acetabular cup version angle. The shaded area indicates the ''safe zone'' for cup version described by Lewinnek et al.[20]. In the revision group, 62% of hips were implanted within this zone.

TABLE III Comparison of Revised Arthroplasties According to Reason for Revision

	Unexplained Pain	Explained Failure	P Value
No. of patients	38	17	
Sex *(female:male)*	24:14	12:5	0.76
Time to revision* *(mo)*	49 (12.0 to 95.0)	41 (12.0 to 121.0)	0.72
Age at time of index arthroplasty* *(yr)*	52.5 (35.0 to 71.0)	55.0 (16.0 to 67.0)	0.84
Blood cobalt level before revision* *(ppb)*	7.2 (0.9 to 167.0)	8.7 (0.9 to 70.0)	0.92
Blood chromium level before revision* *(ppb)*	4.8 (0.4 to 183.0)	6.5 (1.0 to 64.0)	0.70
Head diameter* *(mm)*	46.0 (42.0 to 54.0)	46.0 (38.0 to 54.0)	0.61
Cup inclination angle* *(deg)*	50.0 (24.0 to 69.0)	45.0 (29.0 to 73.0)	0.61
Cup version angle* *(deg)*	17.0 (–13.0 to 45.0)	14.0 (–34.0 to 40.0)	0.80
Cup wear rate* *(μm/yr)*	5.9 (0.3 to 141.0)	8.2 (0.3 to 153.8)	0.71
Head wear rate* *(μm/yr)*	3.4 (0.0 to 52.4)	3.5 (0.8 to 34.1)	0.72

*The values are given as the median, with the range in parentheses.

connected to a Vacutainer system (BD, Franklin Lakes, New Jersey) and trace element blood tubes containing sodium ethylenediaminetetraacetic acid (EDTA). Standard operating procedures were established for cobalt and chromium measurement with use of inductively coupled plasma mass spectrometry (ICPMS) (ELAN DRC II; PerkinElmer, Waltham, Massachusetts). This method was validated against previously published methods in a blinded, inter-laboratory study. Blood samples in the group that underwent revision arthroplasty were obtained immediately prior to removal of the metal-on-metal implants, whereas samples in the "well-functioning" group were all obtained at least one year after the primary arthroplasty.

Wear Analysis of Retrieved Components

The linear wear of each retrieved component was measured with use of a roundness measurement machine (Talyrond 365; Taylor Hobson, Leicester, United Kingdom). The component was mounted and rotated on a spindle

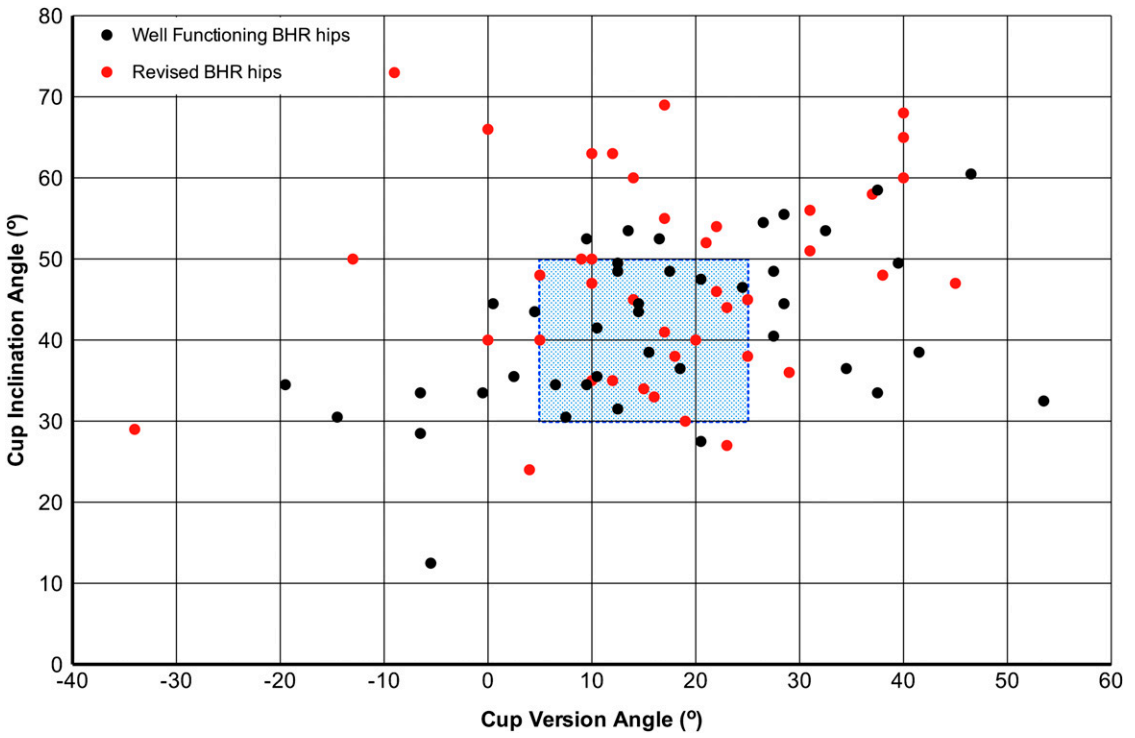

Fig. 3

Scatter plot showing the orientation of each acetabular cup. The shaded box represents the ''safe zone'' for cup orientation described by Lewinnek et al.[20]. In the revision group, 45% of patients had a cup orientation that was within this zone.

TABLE IV Comparison of Arthroplasties Revised Because of Unexplained Pain According to Material Loss Rate*

	Low Material Loss	High Material Loss	P Value
No. of patients	25	30	
Sex *(female:male)*	15:10	21:9	0.40
Time to revision† *(mo)*	47.0 (13 to 121)	42.0 (12 to 95)	0.91
Age at time of index arthroplasty† *(yr)*	51.0 (35 to 71)	56.0 (16.0 to 68.0)	0.10
Blood cobalt level before revision† *(ppb)*	1.9 (0.9 to 3.5)	23.9 (1.0 to 167.0)	<0.01
Blood chromium level before revision† *(ppb)*	2.9 (0.4 to 6.8)	10.26 (0.9 to 183.0)	<0.01
Head diameter† *(mm)*	47.0 (42.0 to 54.0)	46.0 (38.0 to 54.0)	0.08
Cup inclination angle† *(deg)*	48.0 (27.0 to 69.0)	50.0 (24.0 to 73.0)	0.12
Cup version angle† *(deg)*	17.0 (–34.0 to 31.0)	20.5 (–13.0 to 45.0)	0.28
Cup wear rate† *(μm/yr)*	1.6 (0.3 to 5.6)	16.2 (0.3 to 153.8)	<0.01
Head wear rate† *(μm/yr)*	1.5 (0.0 to 3.5)	7.8 (0.0 to 52.4)	<0.01

*A patient with high material loss had a cobalt and/or chromium ion level of >7 ppb and/or a component wear rate of >5 μm/year. †The values are given as the median, with the range in parentheses.

(spindle accuracy, ± 0.02 μm), while a stylus (a 2-mm-diameter ruby) in contact with the component surface measured the deviation from a perfect circle (resolution of stylus gauge, 10 nm).

Three sets of measurements were obtained along the lines of latitude and longitude of each cup and head according to a previously described method[11,12,16]. The raw data were analyzed with use of the Ultra software package (Taylor

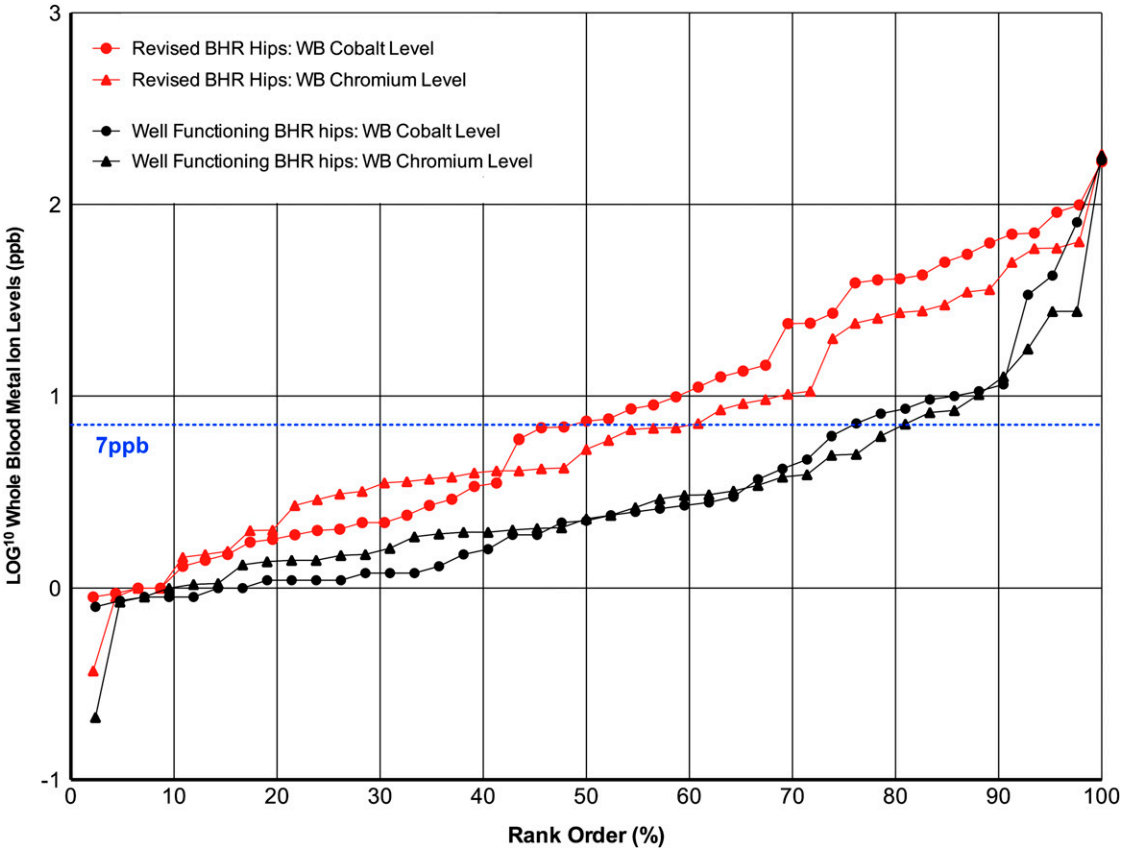

Fig. 4

Graph showing the rank order (expressed as a percentage) of each patient according to the whole blood (WB) metal ion levels. The dotted line at 7 ppb indicates the clinical threshold defined by the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom. In the revision group, the cobalt and chromium levels were below this threshold in 47% and 59% of patients, respectively.

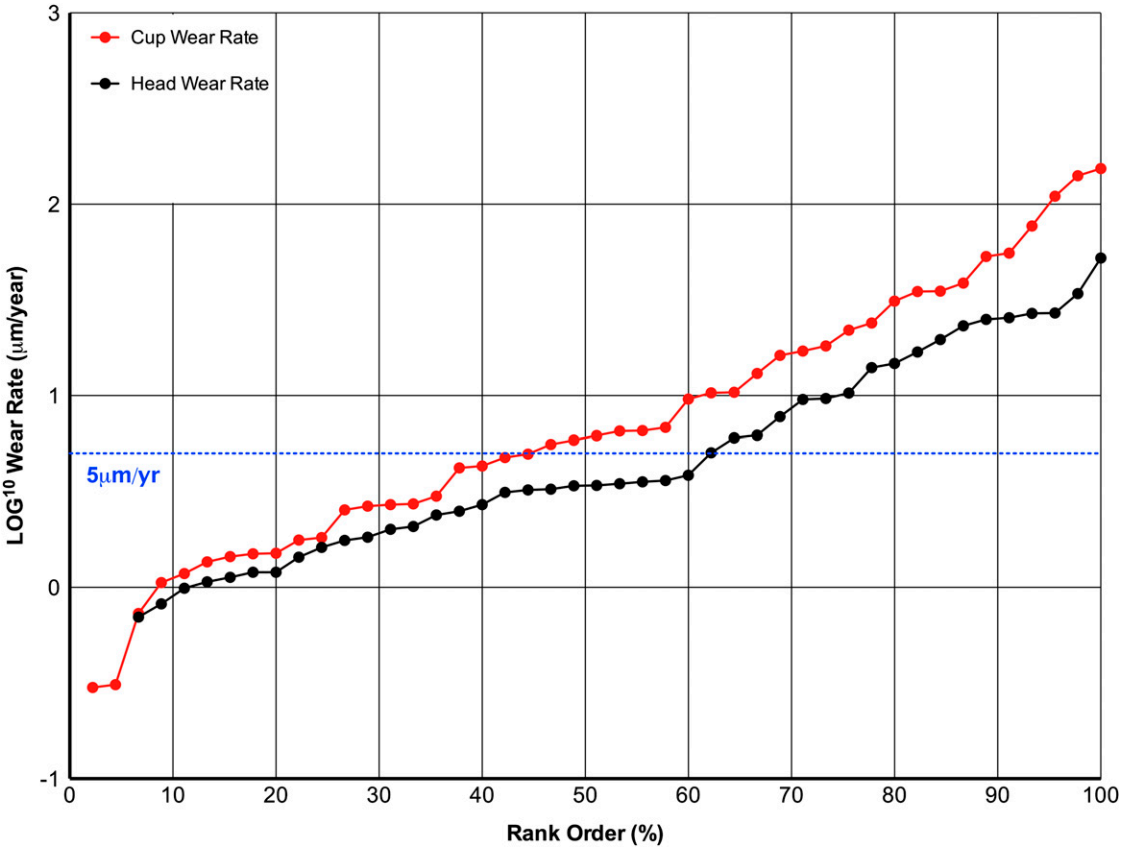

Fig. 5

Graph showing the rank order (expressed as a percentage) of each patient in the revision group according to component wear rate. The dotted line represents a low wear rate of 5 μm/year. According to this definition, 45% of acetabular cup components and 62% of femoral head components in the revision group had low wear.

Hobson) and a customized program written in MATLAB (MathWorks, Natick, Massachusetts). This method allowed us to separate form error from component wear. Form error refers to generalized deviations from the ideal manufactured shape (i.e., nonsphericity of the component), whereas wear is defined as material loss (or transfer). The location, depth, and extent of any worn areas were recorded.

Statistical Methods

Patient, surgical, and implant variables were compared between the group that underwent revision of a BHR hip arthroplasty and the group with a well-functioning BHR arthroplasty. Further subgroup analyses were also performed for the same set of variables. All univariate distributions were tested for normality with use of the Shapiro-Wilk test. The only data that did not demonstrate a normal distribution were blood metal ion levels. The cobalt and chromium levels were therefore logarithmically transformed before comparison, as the logarithms of these levels were normally distributed. For continuous variables, analysis of variance (ANOVA) was initially performed to detect significant differences between groups, primarily between the revised and well-functioning arthroplasty populations. When a significant difference between populations was detected, the Student t test was utilized to evaluate differences between individual pairs of data sets. Contingency analysis with use of the Fisher exact test was performed to compare the proportions of traits between groups. A p value of <0.05 was considered significant in all comparisons.

Results

The reasons for revision in the revised group were unexplained hip pain (in thirty-eight patients), aseptic acetabular cup loosening (in six), aseptic femoral component loosening (in six), component malalignment (in three), and fracture (in two). The comparison between the revised and well-functioning BHR groups is shown in Table I. As shown in Figures 1 and 2, revision was associated with a higher cup inclination angle ($p < 0.01$), but the cup version angle was similar between the two groups ($p = 0.84$). The cup orientation was within the safe zone described by Lewinnek et al.[20] in 45% of the patients in the revised group compared with 38% of the patients in the well-functioning group (Fig. 3). Revision was associated with higher levels of cobalt ($p < 0.01$) and chromium ($p < 0.01$). However, 47% of the patients in the revised group had chromium and cobalt ion levels that were both below the 7 ppb threshold set by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) prior to revision (Fig. 4). Additionally, 54% of the revised components demonstrated wear of <5 μm/year (Fig. 5).

We performed a subgroup analysis within the revised group to compare revisions because of unexplained hip pain with revisions for any other reason. There were no significant differences in any of the variables (Table III), including cup orientation, metal ion levels, and component wear rates. Since unexplained failure has been thought to be associated with

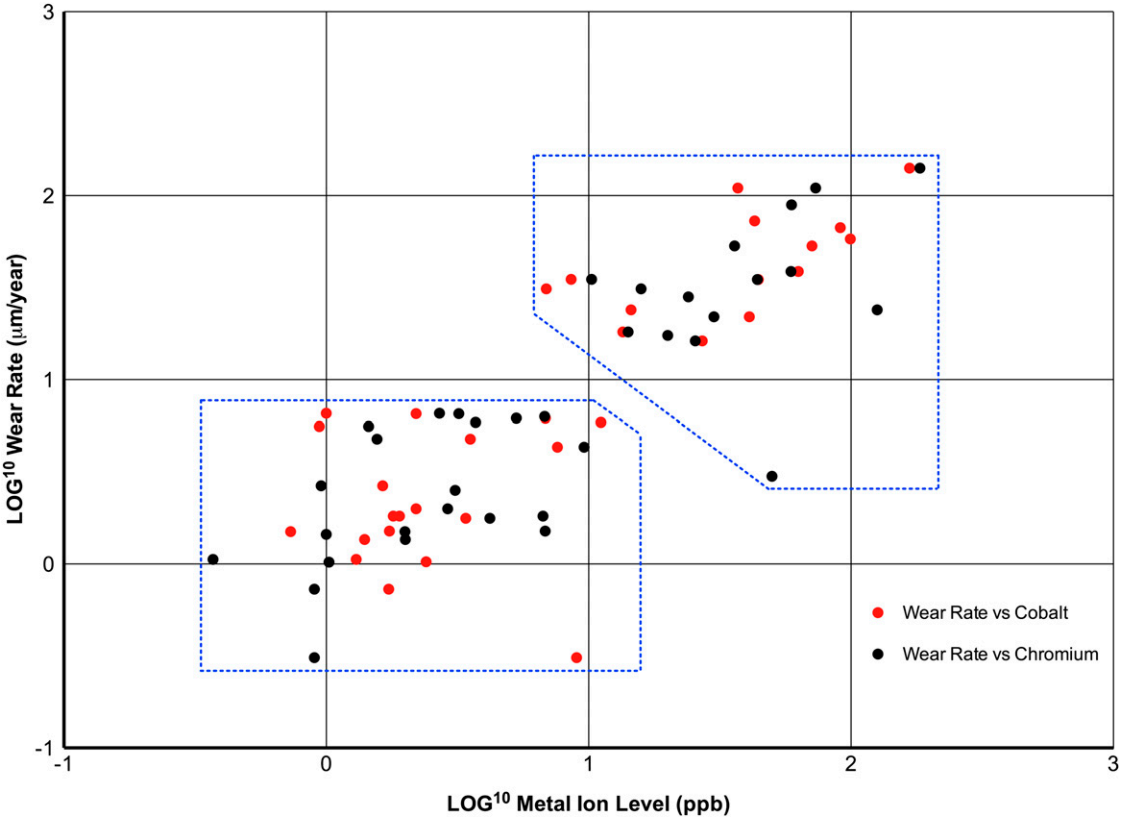

Fig. 6

Scatter plot showing the logarithms of the metal ion levels and wear rate for each patient who underwent revision because of unexplained hip pain. The distribution shows a clear tendency for the patients to fall into two groups: patients with hip pain associated with high wear, and patients with hip pain despite low wear. In fact, 45% of patients with unexplained hip pain demonstrated metal ion levels below the clinical threshold (<7 ppb) and low component wear rates (<5 μm/year).

material loss, we also plotted the wear rate against metal ion levels for the patients who underwent revision because of unexplained hip pain (Fig. 6). There appeared to be two distinct groups of patients—one in whom the failure may have been associated with high wear and elevated metal ion levels, and a second in whom the revision because of unexplained hip pain occurred in the absence of high wear or elevated metal ion levels.

In another subgroup analysis of revisions, patients were categorized according to material loss. The high-loss subgroup was defined as patients with a wear rate (of either or both of the components) that was >5 μm/year and/or a blood metal ion level (of cobalt and/or chromium) that was >7 ppb. No other significant differences were detected between the high-loss and low-loss subgroups (Table IV). For instance, neither acetabular cup inclination nor version was significantly associated with high material loss in patients who underwent revision because of unexplained pain.

Discussion

The current generation of metal-on-metal hip arthroplasty implants has a high failure rate, and many patients undergo revision arthroplasty for a diagnosis of unexplained hip pain. The mechanism that is most commonly cited as being responsible for unexplained hip pain is a high wear rate of the bearing surfaces[21] resulting in a high tissue dose of metal ions and an adverse (inflammatory) tissue reaction[21]. The cause of the high wear rate is thought to involve surgical, design, and patient factors that reduce the extent of femoral head coverage and increase the risk of edge-loading. These factors include a high cup inclination angle[16], a small femoral head diameter[9], and design features such as a reduced articular arc angle of the acetabular cup[6,7,10,11]. However, the pathogenesis of unexplained hip pain remains unclear, particularly given that recent literature has called into question the importance of factors such as cup orientation and material loss[14].

Our study comparing revised and well-functioning metal-on-metal hip arthroplasties involving a single design, the Birmingham Hip Resurfacing System, showed that the majority of revisions were performed following a diagnosis of unexplained hip pain. The study also revealed that failure was associated with a higher acetabular cup inclination angle, a smaller femoral head diameter, and elevated blood metal ion levels. However, revision performed because of unexplained hip pain was not more strongly associated with poor cup orientation or high material loss than revision performed for

other causes was. Additionally, almost one-half (45%) of revisions performed for any reason were in patients who had satisfactory component orientation, acceptable blood metal ion levels, and components with low wear.

More than two-thirds of the revision arthroplasties were performed following a diagnosis of unexplained hip pain. Although we cannot comment on the corresponding failure rates, this proportion is in agreement with data from the National Joint Registry of England and Wales, in which almost one-half of metal-on-metal hip arthroplasty revisions were performed because of unexplained causes including hip pain[2]. Our study also showed that elevated metal ion levels, a steep cup inclination, and a small femoral head diameter were associated with failure of metal-on-metal hip arthroplasties. This is in agreement with the current literature and supports the evidence that reduced femoral head coverage may result in edge-loading, increased wear, and eventually revision of the metal-on-metal hip arthroplasty.

However, despite the fact that clinical failure was significantly associated with steep cup inclination and higher blood metal ion levels, approximately one-half of the patients undergoing revision had a satisfactory cup orientation (within the safe zone described by Lewinnek et al.[20]) and satisfactory metal ion levels (below the threshold suggested by the U.K. MHRA[22]). Additionally, the majority of the retrieved components had low wear. This was true regardless of the reason for revision; revision was not more strongly associated with increased material loss in the subgroup with unexplained hip pain. Given that the present study involved a single hip design, this result would suggest that a considerable proportion of failures because of unexplained hip pain cannot be explained simply by surgical or device factors that lead to excessive wear and elevated metal ion levels. We therefore question the currently accepted theory regarding the pathogenesis of unexplained hip pain and adverse soft-tissue reactions in patients with metal-on-metal hip implants, and we propose that a patient susceptibility factor is responsible for a considerable proportion of hip arthroplasty failures resulting from unexplained hip pain. An analogy may be made to the susceptibility of some patients to osteolysis following metal-on-polyethylene hip arthroplasty[23].

Material loss varied widely among the patients who underwent revision because of unexplained hip pain; patients with high material loss may have experienced pain because of a dose-response inflammatory reaction, and those with low material loss may have experienced pain because they are more susceptible than average (Fig. 5). There is support in the literature for a unifying explanation involving a biocompatibility problem with metal-on-metal hip arthroplasty implants. First, soft-tissue reactions have been reported in patients with several different types of metal-on-metal implants[3-5], although a variety of terminology including aseptic lymphocytic vasculitis-associated lesions (ALVAL), metallosis, adverse reaction to metal debris (ARMD), and pseudotumor have been used to describe the reaction. Second, recent evidence concerning the DePuy ULTIMA metal-on-metal total hip arthroplasty system has brought into question the role of both cup orientation and material loss and has suggested that an unknown patient-specific variable was likely to be responsible for the development of symptomatic soft-tissue reactions[14]. The revision rate in that study was 14%, and the majority of revisions were performed because of unexplained hip pain. As in the present study, more than 50% of patients demonstrated acceptable cup orientation and acceptable metal ion levels, and the majority of retrieved components had low wear. This led the authors of that study to suggest that a subgroup of patients may have had an idiosyncratic immune response to implant-derived metal debris. Other studies have also suggested that metal hypersensitivity may be important[24,25], although there is contradictory evidence regarding this hypothesis[26]. Other immunologically mediated mechanisms have previously been shown to have an underlying genetic component. For example, the existence of links between autoimmune diseases and certain human leukocyte antigen (HLA) types has been established. A good example of such an autoimmune disease is rheumatoid arthritis. Interestingly, rheumatoid arthritis and ALVAL share features of lymphocytic tissue infiltration of the hip capsule and a female bias. A biocompatibility theory does not contradict the published reports of variations in failure rate among metal-on-metal hip implant designs[1]. We suspect that the failure risk results from a combination of a dose-response effect and patient susceptibility. Debris-related failure is likely to occur in all device designs because of patient susceptibility, with higher-wearing designs such as the DePuy ASR[11] having a higher failure rate because of the increase in risk resulting from the dose-response effect. Further retrieval studies comparing different hip implant designs may make it possible to rank implants according to their risk of poor biocompatibility.

The strengths of this study include the large number of patients and retrievals and the recruitment of comparable revised and nonrevised groups. Additionally, the study of a single implant design has allowed us to comment on the surgical and patient variables without confounding by the design differences that exist among the current generation of metal-on-metal hip arthroplasty implants. However, as with any retrieval study, the study also has limitations. It must be emphasized that it is difficult to generalize our results to the entire population of patients with metal-on-metal hip implants. Our results apply only to the BHR system, and the results may therefore be different for other designs. However, it is likely that the clinical variables associated with failure are common to all of the current-generation metal-on-metal hip implants. In addition, diagnosing the reason for revision can be difficult. Diagnosing infection with use of the CRP level and erythrocyte sedimentation rate is particularly difficult since the adverse soft-tissue reactions are known to raise the values of these inflammatory markers.

This study of the Birmingham Hip Resurfacing System indicated that patient susceptibility may be a cause of unexplained hip pain leading to revision arthroplasty. It is essential that future work continue to focus on characterizing this group of susceptible patients. A better understanding could yield biomarkers for patient selection and could help to improve future hip implant designs. In the meantime, unexplained hip

pain remains a common reason for revision arthroplasty and surgeons must closely follow all patients with a metal-on-metal hip implant. ■

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