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J Bone Joint Surg Am. 2005;87:781-787. doi:10.2106/JBJS.D.01820

The Relationship Between Activity and Ions in Patients with Metal-on-Metal Bearing Hip Prostheses

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Background: Total hip replacements with metal-on-metal bearings are frequently implanted in young, active patients. The relationship between patient activity and cobalt and chromium ion levels has not been investigated, to our knowledge.

Methods: Seven patients with well-functioning metal-on-metal bearing hip prostheses and one control subject (no implants), all with normal renal function, were monitored during a two-week-long activity protocol. Lower-extremity activity was continuously assessed with use of a computerized, two-dimensional accelerometer. During the first week, the subjects were requested to limit physical activity. The subjects then completed an hour-long treadmill test followed by a week in which they were encouraged to be as physically active as practically possible. Serum levels of cobalt and chromium ions and urine levels of chromium were assessed at ten time-points during these two weeks.

Results: Regardless of activity, the serum ion levels for a given patient were essentially constant and no correlation was found between patient activity and serum levels of cobalt or chromium, or urine levels of chromium. A mean increase in activity of 28% during the week of high-intensity activity was associated with a mean decrease of 2.7% in the serum cobalt level and a mean increase of 2.0% in the serum chromium level. During the treadmill test, a mean increase in activity of 1621% was associated with a mean increase of 3.0% in the serum cobalt level and a mean increase of 0.8% in the serum chromium level. These results fall within the variability for the measurement accuracy of these tests.

Conclusions: For these patients, serum cobalt and chromium ion levels were not acutely affected by patient activity. Periodic measurements of serum ion levels could be used to monitor the tribologic (lubrication, friction, and wear) performance of a metal-on-metal bearing without adjusting for patient activity. Additional research is needed into the kinetics of ion production, transport, and excretion.

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

For more than thirty years, metal-on-metal bearings used in total hip arthroplasty have demonstrated low wear and have been rarely associated with osteolysis. There have been no reported fractures or other gross material failure, and larger-diameter implants have been found to perform better[1-9]. For these reasons, metal-on-metal bearings have advantages, especially for physically active patients. However, the metal wear particles are nanometers in size and high in number, and their dissolution results in measurable increases in cobalt and chromium ions in the serum, urine, and red blood cells of patients with a metal-on-metal bearing[10-14].

The theoretical risks of higher ion levels include delayed-type hypersensitivity, organ toxicity, and carcinogenesis[15-17]. Since wear of the metal-on-metal bearing is a source of metal ions, active patients, especially if they are young, could be exposed to higher levels of ions for longer periods of time, theoretically increasing their risk.

Studies of serum levels of cobalt and chromium ions have demonstrated variability from patient to patient[12,13]. The levels tend to be higher in the short term and, with a well-functioning prosthesis, the levels may decrease with time[12]. A factor that, at least theoretically, could contribute to the variability in serum ion levels is patient activity. In a pedometer study of 111 patients with well-functioning total joint prostheses, a fortyfold difference in activity was noted between the least active and the most active patient[18]. With use of a computerized, two-dimensional accelerometer, the relationship between patient activity and the wear of polyethylene acetabular bearings has been demonstrated[19].

For these reasons, it seems logical that cobalt and chromium ion levels in patients with metal-on-metal bearings would be positively correlated to patient activity. However, the relationship between changes in patient activity and changes in cobalt and chromium ion levels has not been investigated, to our knowledge. The goal of this study was to test the hypothesis that short-term changes in patient activity are positively correlated to short-term changes in serum cobalt and chromium ion levels.

Materials and Methods

Patients

Seven patients in good health with well-functioning total hip prostheses with a metal-on-metal bearing, at a mean of 17.3 months (range, seven to twenty-five months) postoperatively, and one male control subject provided informed consent to enroll in a study approved by the hospital institutional review board. All participants had normal renal function as determined by serum creatinine levels. There were two women and five men with a mean age (and standard deviation) of 50 ± 11 years (range, thirty-six to sixty-nine years) (see Appendix), a mean weight of 89 ± 20 kg (range, 64 to 125 kg), a mean height of 1.75 ± 0.07 m (range, 1.66 to 1.85 m), and a mean body mass index of 29 ± 5 (range, 23 to 39). The male control subject was thirty-four years old, weighed 100 kg, measured 1.85 m in height, and had a body mass index of 29.2. Lean body mass was calculated by the formula: $(1.10 \times \text{weight}) - 128 \times (\text{weight}^2/[100 \times \text{height}]^2)$ for men and $(1.07 \times \text{weight}) - 148 \times (\text{weight}^2/[100 \times \text{height}]^2)$ for women. It describes patient weight exclusive of body fat[20]. The mean lean body mass in the study group was 62 ± 10 kg (range, 46 to 76 kg). The male control subject had a lean body mass of 62.6 kg.

Three patients had a conventional, cementless total hip replacement, with a press-fit titanium acetabular cup (Pinnacle; DePuy, Warsaw, Indiana), a cobalt-chromium metal liner (Ultamet; DePuy), and a proximally fixed titanium femoral stem (Summit; DePuy) with a 36-mm cobalt-chromium femoral head. One of them had a bilateral total hip replacement with the same design implanted at the same time. The remaining four patients had a nonmodular, metal-on-metal resurfacing arthroplasty (Conserve Plus; Wright Medical Technology, Arlington, Tennessee), with a cementless acetabular cup and a cemented femoral shell with a mean head size of 49 ± 2.2 mm (range, 46 to 52 mm). There were no other sources of metallic ions in these patients and no source of metallic ions in the control subject.

Study Protocol

A two-week test protocol was used to evaluate changes in ion levels (cobalt and chromium) as a result of low-intensity activity (over one week), acute high-intensity activity (a treadmill test), and high-intensity activity (over one week). Activity during this two-week period was quantitatively assessed with use of a computerized, two-dimensional accelerometer (StepWatch Activity Monitor; Cyma, Seattle, Washington) worn on the ankle, following methods described previously[18,19,21-23]. To facilitate comparisons, all patient activity data in this study were extrapolated and reported as cycles per year.

Needles, intravenous lines, and utensils used for blood collection were previously tested to ensure that they were free of metal contamination. The first 5 mL of obtained blood was discarded. The initial flow of blood effectively flushed the tubing, removing detachable contaminants.

On the first day, two blood samples and a twenty-four-hour urine sample were collected and were used to measure baseline levels of cobalt and chromium in serum and chromium in urine. Urine cobalt was not tested because the detection limit for cobalt with our method is higher than that of chromium. Additionally, routine blood tests were obtained on this day in order to ensure normal renal function. The subjects then started the week of low-intensity activity. During this week, they were instructed to be as inactive as possible, avoiding exercise, long walks, and sports activities. On day 8, they returned to the clinic and had an intravenous line inserted. Two blood samples and a spot urine sample were collected to determine the serum levels of cobalt and chromium and urine chromium after the week of low-intensity activity.

The subjects then started the treadmill test, walking and running on the treadmill as fast as their physical condition allowed for sixty minutes. The speed and speed changes during the test were recorded. Blood samples were obtained at fifteen, thirty, forty-five, sixty, ninety, and 120 minutes after the start of the test. The subjects collected the first urine sample after the treadmill test and an additional sample that same evening before they went to bed. Additionally, two blood samples and a urine sample were obtained the next morning after the treadmill test.

The week of high-intensity activity followed the treadmill test. The subjects were instructed to be physically active and exercise as much as practically possible. At the end of one week, blood and urine samples for the high-intensity activity week were collected. A total of fourteen blood samples and six urine samples were obtained from each subject.

Trace Metal Analysis

After collecting and preparing the blood in a centrifuge, the serum was separated from the clotted fraction with a validated technique[24]. The concentrations of cobalt and chromium in serum and the concentration of chromium in urine were measured with graphite-furnace Zeeman atomic absorption spectrophotometry[25]. The detection limits, in parts per billion, were 0.3 for cobalt in serum, 0.03 for chromium in serum, and 0.015 for chromium in urine.

Statistical Analysis

With use of a statistical software package (Stata, version 7.0;

Stata, College Station, Texas), the 95% confidence intervals and standard errors for the percentage difference in activity, serum cobalt levels, and serum chromium levels between the week of low-intensity activity, the week of high-intensity activity, and the treadmill test were calculated. The influence of independent variables on serum levels of cobalt and chromium was assessed with univariate regression analysis.

Results

Activity

During the week of low-intensity activity and the week of high-intensity activity, the patients recorded an extrapolated mean (and standard deviation) of 2.02 ± 0.72 million cycles per year (range, 1.12 to 2.93 million cycles per year) and 2.51 ± 0.78 million cycles per year (range, 1.56 to 3.87 million cycles per year), respectively (see Appendix). This represents a mean increase (and standard error of the mean) in activity of 28% ± 6% (95% confidence interval, 13% to 43%) during the week of high-intensity activity compared with the week of low-intensity activity.

During the hour-long treadmill test, the patients recorded a mean of 3525 cycles, which extrapolates to a mean (and standard deviation) of 31 ± 2.89 million cycles per year (range, 27.1 to 34.6 million cycles per year). Compared with the mean activity of the week of low-intensity activity, the mean activity (and standard error) on the treadmill test represents an acute increase of 1621% ± 265% (95% confidence interval, 972% to 2271%) (see Appendix).

Serum Cobalt

The mean variability (and standard deviation) in the levels of cobalt in serum between the two samples obtained from each patient at each time-point was 6.0% ± 5.4%. Figure 1 graphically displays all of the serum cobalt levels over the course of the activity protocol from baseline through the high-intensity activity week. The levels of serum cobalt in the control subject were always below the detection limit (0.3 part per billion). At the end of the week of low-intensity activity, the mean serum cobalt level for all of the patients was 1.40 ± 0.85 parts per billion (range, 0.81 to 3.22 parts per billion) (Fig. 1 and Appendix). One patient, with a bilateral total hip replacement, had the highest level of cobalt in serum, which was about twice as high as the average for the other patients. At the end of the week of high-intensity activity, the mean level of serum cobalt for all patients was 1.29 ± 0.63 parts per billion (range, 0.90 to 2.68 parts per billion). The levels of serum cobalt decreased by a mean (and standard error) of 2.7% ± 4.7% (95% confidence interval, –14.2% to 8.9%) per patient during the week of high-intensity activity compared with those during the week of low-intensity activity. Three of the seven patients demonstrated a decrease in serum cobalt after the week of high-intensity activity compared with that after the week of low-intensity activity.

A mean serum cobalt level (and standard deviation) of 1.41 ± 0.79 parts per billion (range, 0.81 to 3.12 parts per billion) was measured for all patients during the treadmill test. Compared with the serum cobalt levels obtained after the week of low-intensity activity, this represents a mean increase of

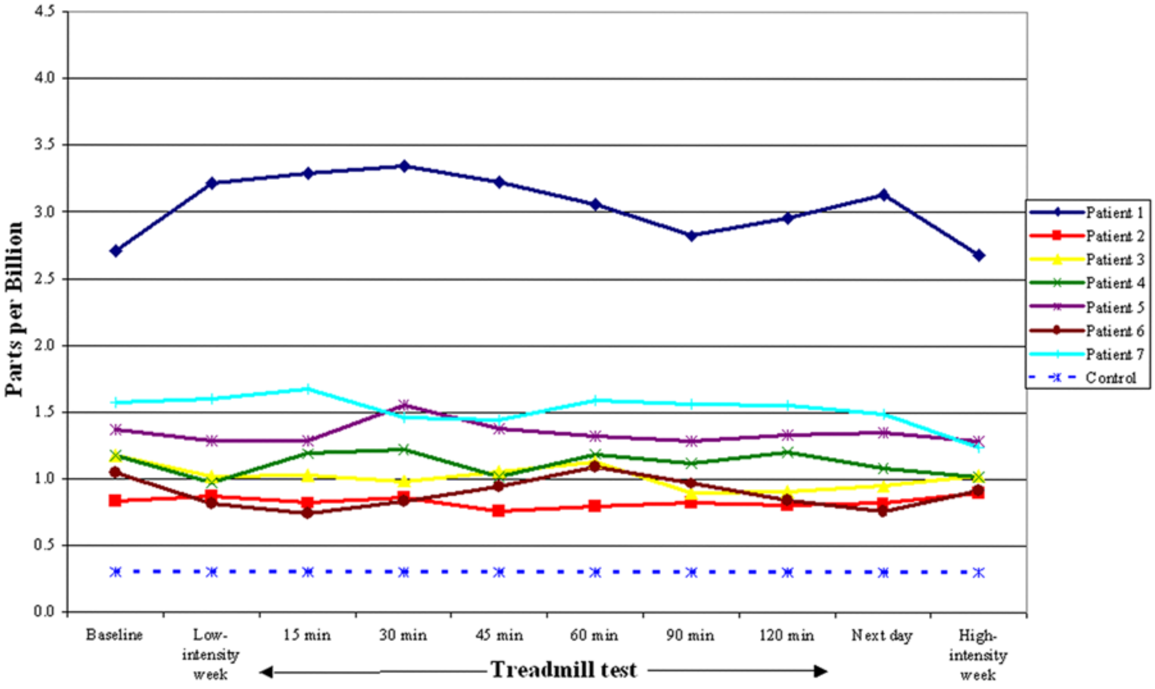

Fig. 1

Graph showing the serum cobalt levels for ten time-periods over the course of the activity protocol. Compared with the level during the low-intensity activity week, the level of serum cobalt increased by a mean of 3.0% per patient during the treadmill test and decreased by a mean of 2.7% per patient during the week of high-intensity activity. Note the patient-to-patient variability.

3.0% ± 3.6% (95% confidence interval, –5.7% to 11.7%) per patient in levels of cobalt in serum. Four of the seven patients demonstrated a decrease in serum cobalt after the treadmill test compared with the level after the week of low-intensity activity.

Serum Chromium

The mean variability (and standard deviation) in the levels of chromium in serum between the two samples obtained from each patient at each one of the time-points was 1.5% ± 1.4%. At the end of the week of low-intensity activity, the mean level of serum chromium for all patients was 2.08 ± 0.90 parts per billion (range, 1.34 to 3.8 parts per billion) (Fig. 2 and Appendix). One patient, who had a bilateral total hip replacement, had the highest level of serum chromium, which was about twice the average for the other patients. At the end of the week of high-intensity activity, the mean level of serum chromium for all patients was 2.12 ± 0.87 parts per billion (range, 1.24 to 3.62 parts per billion). The levels of serum chromium at the end of the week of low-intensity activity and the week of high-intensity activity in the control subject were 0.06 and 0.04 part per billion, respectively. The levels of serum chromium in the patients increased by a mean (and standard error) of 2.0% ± 3.0% (95% confidence interval, –5.3% to 9.3%) per patient during the week of high-intensity activity compared with that during the week of low-intensity activity. Three of the seven patients showed a decrease in serum chromium after the week of high-intensity activity compared with that after the week of low-intensity activity.

The mean serum chromium level (and standard deviation) for all patients during the treadmill test was 2.11 ± 0.93 parts per billion (range, 1.29 to 3.79 parts per billion). This represents a mean increase of 0.8% ± 1.7% (95% confidence interval, –3.5% to 5.0%) per patient compared with that after the week of low-intensity activity. Three of the seven patients showed a decrease in serum chromium after the treadmill test compared with that after the week of low-intensity activity.

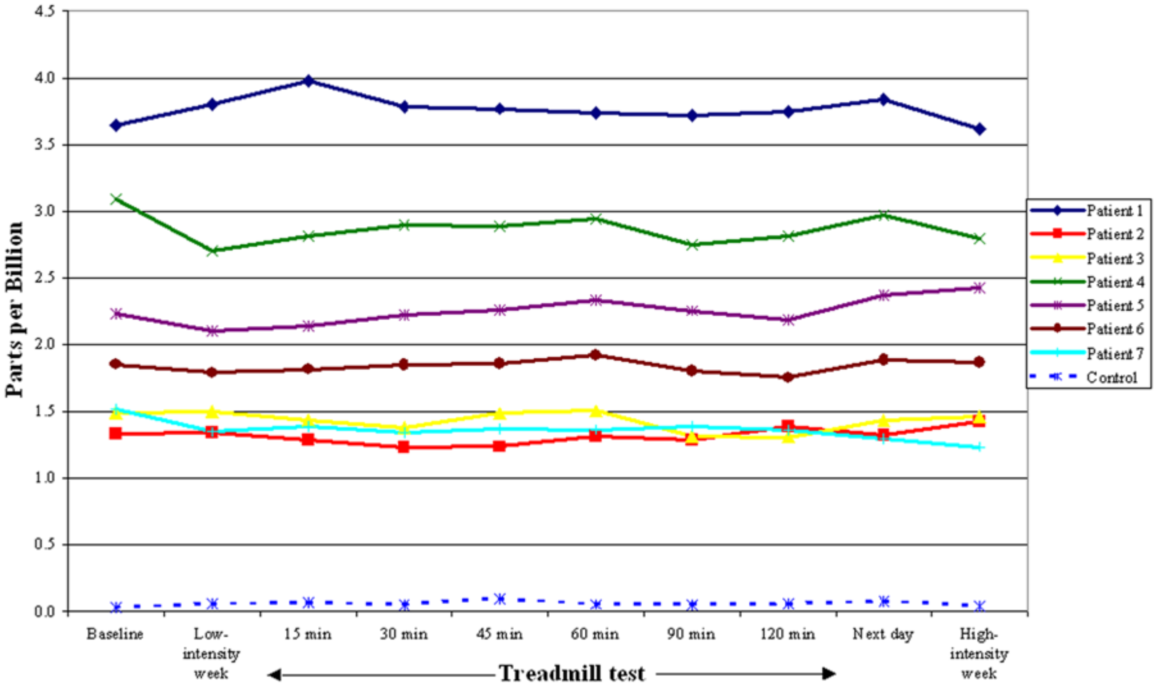

Fig. 2

Graph showing the serum chromium levels for ten time-periods over the course of the activity protocol. Compared with the level during the week of low-intensity activity, the level of serum chromium during the treadmill test and the week of high-intensity activity increased by a mean of 0.8% and 2.0% per patient, respectively. Note the patient-to-patient variability.

Urine Chromium

The chromium levels in urine were highly variable. A mean level (and standard deviation) of 2.17 ± 2.15 parts per billion (range, 0.26 to 5.8 parts per billion) was measured at the end of the week of low-intensity activity. The mean level of chromium in urine measured at the end of the week of high-intensity activity was 2.51 ± 2.09 parts per billion (range, 0.49 to 6.81 parts per billion). The levels of chromium in urine measured after the treadmill test were 3.08 ± 2.56 parts per billion (range, 0.28 to 6.87 parts per billion). No consistent relationship was detected between serum chromium and urine chromium levels (p = 0.22).

Activity and Ion Levels

No correlation was found between baseline patient activity and serum levels of cobalt (r = 0.06; p = 0.81) or serum (r = 0.02; p = 0.92) or urine levels of chromium (r = 0.16; p = 0.47). A mean increase (and standard error) in activity of 28% ± 6% (95% confidence interval, 13% to 43%) during the week

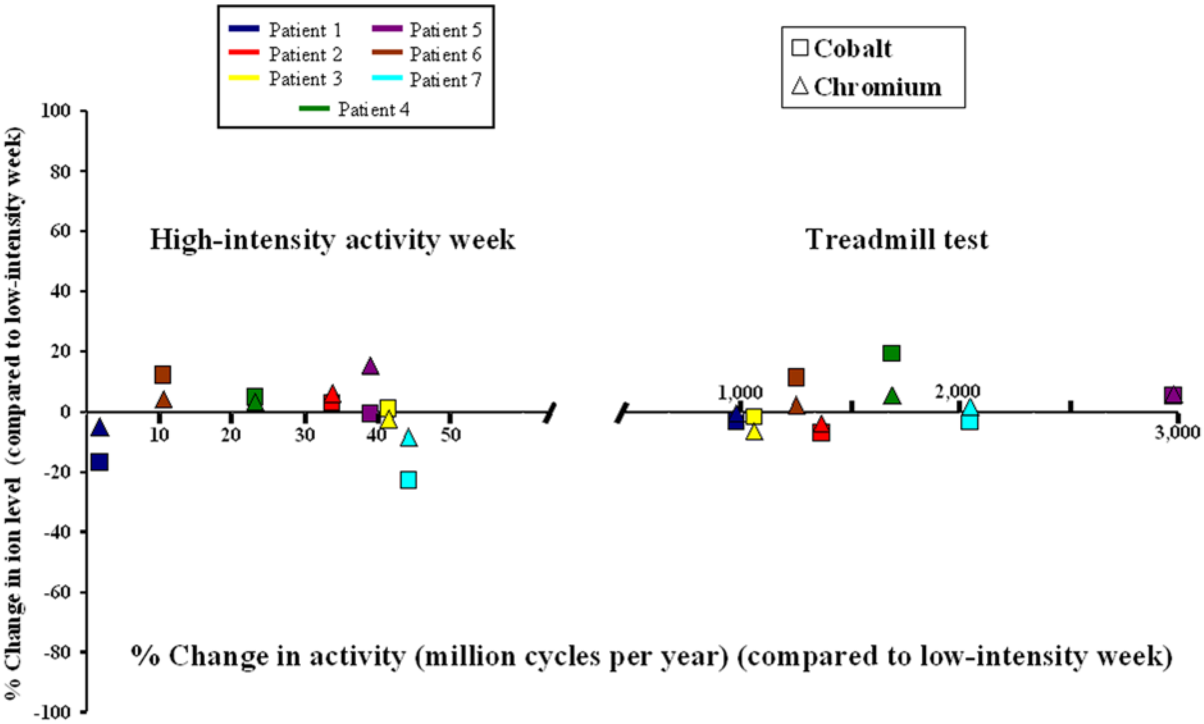

Fig. 3

Graph showing the changes in serum cobalt and chromium levels relative to activity. A mean increase in activity of 28% during the week of high-intensity activity was associated with a mean decrease of 2.7% in serum cobalt and a mean increase of 2.0% in serum chromium. A mean increase in activity of 1621% during the treadmill test was associated with a mean increase of 3.0% in serum cobalt and a mean increase of 0.8% in serum chromium.

of high-intensity activity was associated with a mean decrease of 2.7% ± 4.7% (95% confidence interval, –14.2% to 8.9%) in serum cobalt and a mean increase of 2.0% ± 3.0% (95% confidence interval, –5.3% to 9.3%) in serum chromium. During the treadmill test, a mean increase of 1621% ± 265% (95% confidence interval, 972% to 2271%) in activity was associated with a mean increase of 3.0% ± 3.6% (95% confidence interval, –5.7% to 11.7%) in serum cobalt and a mean increase of 0.8% ± 1.7% (95% confidence interval, –3.5% to 5.0%) in serum chromium (Fig. 3). These results effectively constitute no change in serum ion levels for these changes in activity because the values are within the variability for the measurement accuracy of these tests. No correlation was found, on the basis of the numbers, between age, gender, length of follow-up, weight, height, body mass index, lean body mass, and component head size and the levels of cobalt or chromium in serum or urine chromium.

Discussion

These data indicate that, within the conditions and range of activity in this study, serum cobalt and chromium ion levels are minimally affected by activity. For the ten time-points that serum ions were measured for each patient during the two weeks of the activity protocol, the levels for each patient were nearly constant. There was, however, substantial variability in the ion levels from patient to patient.

The levels of cobalt and chromium ions are a function of ion production, transport, and excretion, but little is known about the kinetics of these processes. The dominant source of ion production in these patients is wear of the cobalt-chromium-alloy bearing. While there may be some contribution from the modular connections in the total hip prostheses and some contribution from the porous coating of the resurfacing implants, previous work has indicated that the amount of ions generated from such sources is small compared with that from the cobalt-chromium bearing[14].

Cobalt and chromium are excreted by the kidneys with negligible loss by means of sweat and stool[26]. The urine chromium values in this study were variable. The patients had unrestricted and unmonitored fluid intake. Intrapatient and interpatient variability in urine chromium concentration is a function of maintaining free-water balance. It is not known whether there are individual differences in the renal clearances of cobalt and chromium ions. The loss of renal function results in a rapid increase in serum cobalt and chromium ion levels[27].

The report of elevated serum ion levels in a patient with a metal-on-metal total hip prosthesis following a marathon[28] is not necessarily in conflict with the findings in the present study; rather, it emphasizes the role of normal renal function and free-water balance upon serum ion levels. During a marathon, fluid is lost through sweat and pulmonary ventilation with little production of urine. With adequate rehydration and urine production, serum ion levels decrease[28]. Serum ion levels change in response to stress[29,30]. The effect of physical stress on serum cobalt and chromium ion levels is not known but may contribute to the transient increase seen with the stress of running a marathon.

Wear of a metal-on-metal bearing cannot be measured radiographically[7]. Serum cobalt or chromium ion levels could be a means to assess the tribologic (lubrication, friction, and wear) performance of the bearing[31]. Such a test would have less value for assessment of bearing performance if the serum ion levels were closely correlated to patient activity, especially acute activity. If activity were closely correlated to serum ion levels, then an accurate, concomitant measure of activity would be needed to normalize the ion results before any statements could be made regarding the tribologic performance of the bearing, as has been done with polyethylene wear[19].

With normal renal function and free-water balance, an increase in serum ion levels should be indicative of some problem in the system, including an alteration in renal excretion, corrosion (taper and/or bearing), wear of other surfaces (such as from impingement), an increase in primary bearing wear rate from a change in the wear mechanism due to third bodies (from impingement or loosening), or a change in component orientation (due to loosening), or a change in the lubrication regimen.

Insight into an explanation for the patient-to-patient variability in serum ion levels can be gained from wear simulator tests and retrieval analyses. In hip simulator tests of metal-on-metal bearings, the first 200,000 to two million cycles have been characterized by a relatively rapid wear rate during the so-called run-in phase, which results in smoother surfaces, larger contact area (lower contact stress), better lubrication, and lower wear[4,32]. The wear rate and the duration of the run-in phase are sensitive to manufacturing variables but run-in wear generally represents >90% of all the wear generated by that bearing.

The bearing then enters a steady-state mode that is characterized by minimal wear[4,32]. Wear rate in the steady state is a small fraction of the wear rate during the run-in phase. The wear rate of metal-on-metal bearings retrieved after a year or less in vivo is more than five times higher than that seen on bearings retrieved after three or more years[8], and bearings retrieved after more than twenty years have only a couple of micrometers of wear per year[7,33-35].

The clinical implication of these tribologic characteristics is that the great majority of wear particles are generated during the run-in phase[4,32,34]. It is our hypothesis that serum ion levels are a function of the volume of wear particles generated. Because the great majority of wear occurs during the run-in phase, the volume of wear particles generated during the run-in phase is an important determinant of serum cobalt and chromium ion levels. The dissolution over time of this initial shower of wear particles contributes the great majority of ions and establishes the serum ion levels for that patient. Ion data from patients with well-functioning hips with metal-on-metal bearings that have been in situ for more than twenty years suggest that the serum cobalt and chromium ion levels slowly decrease as the volume of particles dissolves over time[12,33].

Even with *identical* components (there is slight variability in manufacturing tolerances), it is likely that there is variability in wear during the clinical run-in phase because of variability in component positioning, variability in the loads and motions of the joint in a specific patient, and variability in the lubrication regimens in vivo. Variability in the in vivo conditions can account for or contribute to patient-to-patient variability in serum ion levels. Differences in physiology, such as the efficiency of excretion, could also account for or contribute to patient-to-patient variability in serum ion levels.

There are several limitations of this study. Due to the intensity of the protocol, subject recruitment was limited. The patients were, however, representative of those who are currently considered candidates for a metal-on-metal bearing[18]. The ion levels were reproducible and similar to those in other reports[12-14]. We did not monitor fluid intake and output, which limits the interpretation of the urine ion values, the rate of serum-to-urine ion transfer, and the rate of ion production. It was simply impractical to monitor fluid balance in these patients for two weeks. We do not know whether larger or longer changes in activity would have any effect on ion levels, or whether an acute increase in activity results in higher ion levels after two weeks.

Appendix

Tables presenting data on the demographic characteristics, activity, and serum cobalt and chromium levels for the individual patients during the study are available with the electronic versions of this article, on our web site at 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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In support of their research or preparation of this manuscript, one or more of the authors received grants or outside funding from Wright Medical Technology and the Piedmont Fund of the Los Angeles Orthopaedic Hospital Foundation. In addition, one or more of the authors received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity (DePuy Orthopaedics). No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or nonprofit organization with which the authors are affiliated or associated.

doi:10.2106/JBJS.D.01820

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