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Serum and urine metal levels in patients with metal-on-metal surface arthroplasty

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The resurgence of metal-on-metal articulating surfaces for hip arthroplasty has also heightened concerns about the degree and magnitude of metal particle generation and the accompanying increase in circulating metal ion concentrations. In this study, we measured the concentration of chromium in serum and urine and the concentration of cobalt in serum in twenty-five patients with modern metal-on-metal surface arthroplasty of the hip in a prospective manner. The results showed that the mean post-operative chromium in serum levels were 22-fold, 23-fold and 21-fold higher at 3, 6 and 12 months post-operative, respectively, than pre-operative levels. The mean post-operative cobalt in serum levels were 8-fold, 7-fold and 6-fold higher at 3, 6 and 12 months post-operative, respectively, than pre-operative levels. The mean post-operative chromium in urine levels were 9-fold, 10-fold and 14-fold higher at 3, 6 and 12 months post-operative, respectively, than pre-operative levels. The values seen in this study with the current generation of surface arthroplasties are: (a) lower than those seen in an earlier generation of surface arthroplasties; (b) in the same range as those observed in association with metal-on-metal conventional total hip replacements, which typically have smaller head sizes; (c) higher than values observed in patients with conventional metal-on-polyethylene articulating couples.

Introduction

Surface arthroplasty of the hip is a conservative procedure designed to retain valuable femoral bone stock in the younger and more active patient. The procedure was introduced in the late 1940s and early 1950s [1–3] during the formative years of hip arthroplasty. The use of polyethylene, metal head shells and poly methyl methacrylate for fixation resulted in its increased popularity and by the late 1970s a number of designs were available for use [4–12]. By the early 1980s, however, high rates of failure [13–19] (in most instances due to factors unrelated to the bearing), and the more successful results with conventional hip arthroplasty resulted in the near abandonment of this technique [1, 3, 20, 21].

Metal-on-metal articulation was available for general use in the 1960s [22, 23] and of the early surface arthroplasty designs several were of the metal-on-metal type [4, 7]. The clinical results with these designs were also unsatisfactory and their use was abandoned.

With the reintroduction of metal-on-metal bearing surfaces for total hip replacements with improved manufacturing and material properties in 1988 [24] new metal-on-metal designs for surface arthroplasty were also reintroduced. The Wagner Type [25] was first implanted starting in 1991, and it consisted of forged CoCrMo alloy articulating surfaces, which were mounted into a Ti coarse blasted contoured shell for osseointegration. The McMinn Type [3] was manufactured from cast CoCr alloy. The acetabular component was coated with hydroxyapatite on its outer surface and was meant for cementless fixation, the femoral component was a chamfered cylinder with a short stem to assure correct alignment into the femoral neck and was cemented into place. The third type was developed by one of the authors (HCA) and is the implant under study here. It is the Conserve® Plus by Wright Medical Technology, Inc. (Fig. 1). The acetabular component is designed for cementless fixation. It consists of one piece and has sintered beads on the outer surface designed for interference fitting to obtain initial stability. The femoral component is a hemispheric shell with a chamfered cylindrical interior design and a short tapered stem to enhance alignment and stability. It is meant for cemented fixation.

A consequence of articulation is wear, regardless of the articulating couple [26–30]. This wear leads to accumulation of wear particles in the periprosthetic tissues which can cause foreign body reaction and lead to

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implant loosening and osteolysis. Polyethylene particles are now considered to be the main causes of aseptic loosening through this process of wear-induced osteolysis. Metal wear particles can also cause local tissue reactions and their corrosion can lead to increased metal ion release into the body. The effects of metal particles and their corrosion products locally and systemically are being studied through the examination of retrieval and autopsy specimens. Doorn *et al*. [31] reported that the periprosthetic tissue inflammation was less marked around metal-on-metal joints compared with metal-on-polyethylene joints. However, Willert *et al*. [32] have noted unusual histological features in the periprosthetic tissues around total hips with Metasul® bearings that are similar to delayed type hypersensitivity reactions. Similar findings have been noted in other metal-on-metal designs [33]. Metal particle migration from total hip implants with metal-on-polyethylene bearings has been reported by several authors [34, 35] and it is agreed that the problem is greater with loose implants. Our own experience with a 30-year McKee-Farrar metal-on-metal hip examined at autopsy showed minimal particle migration to the organs [36].

Studies have shown that well-functioning modern metal-on-metal articulating couples wear at a much lower rate than metal-polyethylene couples, and have a linear wear rate in the range of 5–9 µm per year [37–39]. However, studies have also shown that metal-on-metal couples have a much higher wear rate during the first year of service [40]. This may be of particular concern with the surface arthroplasty due to higher frictional torques and greater sliding distances resulting from the larger head sizes. While linear penetration rates and volumetric wear rates are lower with metal-on-metal bearings these bearings are associated with increased metal release in comparison to conventional metal-on-polyethylene bearings [41].

Trace metal analysis has been used in recent years to gauge the functionality of total hip replacements. Elevated serum and urine metal levels in patients with well functioning metallic implants have been previously reported [41–44] and patients with loose implants were found to generate higher metal levels [45–47].

The purpose of this study was to determine the concentration of chromium in serum and urine and the concentration of cobalt in serum in patients with a new generation metal-on-metal surface arthroplasty.

Figure 1 Conserve® Plus surface arthroplasty (Wright Medical Technology, Inc., Arlington, TN, USA).

Materials and methods

Twenty-five patients with metal on metal surface arthroplasty of the hip were studied (Table I). Thirteen of the twenty-five patients were sampled prior to their surgery and post-operatively at one or more intervals. The remaining cases were sampled at various time periods following surgery (Tables II–IV). The implants were inserted at the Joint Replacement Institute at Orthopedic Hospital in Los Angeles by two senior surgeons (HCA and TPS). The patient population, however, is from across the United States. An effort was made to sample the patients at pre-determined time periods but as can be seen in Tables II–IV this was not always possible. All cases had only one metal-on-metal implant at the time of sampling.

All twenty-five patients received the Conserve® Plus type surface arthroplasty of the hip (Fig. 1). The femoral component was cemented. The head size ranged from 38 to 52 mm. The acetabular component was cementless with an outer diameter range of 48–62 mm. Both the acetabular and femoral components were manufactured by Wright Medical Technology, Inc (Arlington, TN). There were 17 males and 8 females with an average age at implantation of 49 years (range 28–62 years). Patient demographic data is shown in Table I. The indication for surface arthroplasty surgery was osteoarthritis for 21 patients, avascular necrosis for three patients, and melorheostosis for one patient. At this time of this report, the patients had excellent clinical results; one patient had an osteolytic lesion in the femoral neck, but was asymptomatic and the remaining had excellent radiographic results.

Sample collection

Blood was collected into S-Monovettte syringes using the multi-adapter (Sarsedt, Priceton, NJ) and a butterfly infusion set (Abbott, Abbott Park, IL). Three ten-milliliter syringes were drawn and each syringe was labeled to indicate the sequence of collection. The first 10 ml were drawn to rinse the needle and adapter, as a precautionary measure. Blood was allowed to clot naturally, centrifuged and separated into cell and serum fractions and stored in labeled vials at $-80\,^{\circ}C$ until analysis.

TABLE I Demographic data

Case	Sex	Age (at surgery)	Side	Head size (mm)	Acetabular O.D. (mm)
1	M	62	L	52	62
2	M	38	L	50	60
3	M	51	R	44	54
4	M	47	L	52	62
5	M	28	R	52	62
6	F	33	L	40	58
7	M	58	L	48	58
8	M	55	L	50	60
9	F	45	L	44	56
10	M	38	R	52	62
11	M	59	L	50	60
12	F	38	L	44	54
13	M	61	L	50	60
14	F	55	L	40	50
15	M	52	L	52	62
16	M	48	L	48	58
17	M	53	L	50	60
18	F	53	R	42	52
19	F	61	R	46	56
20	M	56	R	48	58
21	F	49	R	42	62
22	M	55	R	50	60
23	F	36	L	38	48
24	M	46	L	52	62
25	M	39	R	52	62
Mean		**49**		**48**	**58**

TABLE II Serum chromium concentration (ng/ml (ppb))

Case	Pre-op	3 months	6 months	12 months
1		4.52	4.22	2.43
2			1.10	
3		1.63		1.23
4			1.13	1.12
5			2.03	1.43
6	0.04	2.68	3.76	1.55
7	0.05	1.27	1.28	2.38
8	0.02			0.73
9	0.04	1.39		2.15
10	0.06	2.27		0.87
11	0.08	2.14		
12		1.72		1.73
13			0.62	0.77
14	0.15	2.38	1.04	
15		1.12	1.19	0.89
16	0.24			2.93
17	0.11	1.45		1.48
18				3.57
19	0.15	1.16		1.16
20		2.20		2.76
21		1.06		1.76
22	0.08	2.26		
23		0.27		0.59
24	0.07	2.38		4.33
25	0.04		3.83	2.01
Mean ± 95% C.I.	**0.08 ± 0.04**	**1.88 ± 0.48**	**2.02 ± 0.98**	**1.80 ± 0.45**

Subjects were provided with polypropylene containers and detailed instructions for a contemporaneous 24-h urine sample, whenever possible. In addition, women were provided with Specipans (Plasti-Products, Omaha, NB) from which urine was transferred into the polypropylene containers. Samples of urine were labeled and frozen at $-80\,^{\circ}C$ until analysis.

All collection containers, syringes and apparatuses were acid washed and verified to be contamination free. All manipulations of the specimens following collection were carried out in a class-100 environment provided by a SterilGuard Biological Safety Cabinet (Baker, Sanford, MN) using class-100 gloves (Oak Technical, Ravenna, OH) to minimize atmospheric and manual contamination.

Metal ion analysis

Quantitative analysis was performed with a Zeeman-5100 atomic absorption spectrophotometer with an HGA-600 heated graphite furnace and an AS-60 autosampler (Perkin-Elmer, Norwalk, CT). All samples were tested in triplicate. The detection limits were 0.03 ng/ml for chromium in serum, 0.015 ng/ml for chromium in urine and 0.3 ng/ml for cobalt in serum.

Statistical analysis

Data are presented descriptively due to the preliminary nature of this study. To facilitate data interpolation, time periods between 2 and 4 months were consolidated into a 3 month value, time periods between 5 and 7 were consolidated into a 6 month value. Concentrations below the detection limit were assigned, by convention, a value of one-half the detection for each element/matrix. Means at each time interval were computed to provide a relative scale for discussion. Longitudinal comparisons (for pre-op, 3 and 12 months post-operative time periods) were made using the Friedman test followed by the Sign test when the former test indicated a level of significance of $p < 0.05$. Due to the limited number of cases available that included the 6 month post-operative time period, this time period was not included in the longitudinal statistics. Correlations for the cases available were established with use of the Spearman rank-order correlation test.

Results

Serum and urine metal levels for each case are shown in Tables II–IV and Fig. 2. As can be seen, the mean serum chromium concentrations (SrCr) increase up to 6 months post-operative and then begin to decrease. Serum cobalt (SrCo) levels increase up to 3 months post operative and then begin to decrease. There was a strong correlation between SrCr and SrCo levels at 3 months ($r = 0.887$, $p < 0.001$, Spearman rank-order correlation test), 6 months ($r = 0.794$, $p = 0.006$, Spearman rank-order correlation test) and 12 months ($r = 0.910$, $p < 0.001$, Spearman rank-order correlation test) post operatively.

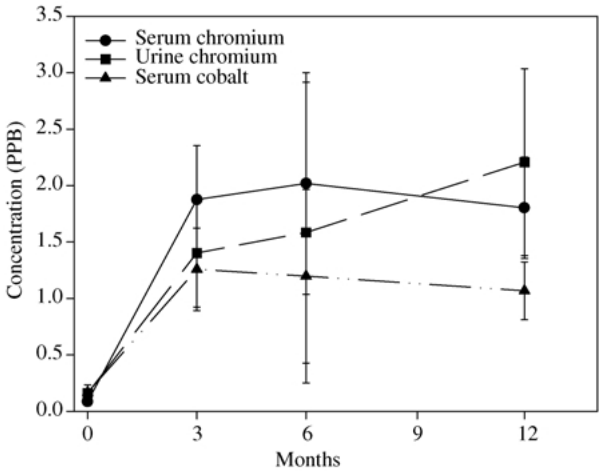

Figure 2 Serum and urine metal concentrations in patients with Conserve® Plus surface arthroplasty. Mean ± 95% confidence interval.

Urine chromium (UrCr) levels tended to increase with time. The mean levels at 3, 6 and 12 months post-operative, are higher than the mean pre-operative level. UrCr levels at 3 and 12 months post-operative were statistically higher than pre-operative levels ($p < 0.01$, Sign test), and UrCr levels at 12 months post operative were statistically higher than 3 months post-operative levels ($p = 0.013$, Sign test). There was a strong correlation between SrCr and UrCr at 6 months

TABLE III Urine chromium concentration (ng/ml (ppb))

Case	Pre-op	3 months	6 months	12 months
1		2.40	2.85	4.61
2			0.54	
3		0.54		1.24
4			0.71	0.97
5			1.73	1.47
6	0.08	0.49	0.65	0.86
7	0.05	0.67	0.90	2.31
8	0.01	0.73		0.83
9	0.42	1.39		2.33
10	0.36	2.79		
11	0.16	1.87		3.01
12	0.10	0.27		0.93
13				2.43
14	0.10		0.53	
15		0.98	0.63	1.03
16	0.04	0.66		2.29
17	0.16	2.61		1.72
18				5.70
19	0.17			0.43
20		1.28		2.07
21		1.05		0.52
22	0.21	3.05		
23				
24	0.32			7.17
25	0.09	1.68	5.73	2.23
Mean ± 95% C.I.	**0.16 ± 0.07**	**1.40 ± 0.48**	**1.58 ± 1.33**	**2.21 ± 0.83**

TABLE IV Serum cobalt concentration ng/ml (ppb)

Case	Pre-op	3 months	6 months	12 months
1		3.04	3.50	2.10
2			0.41	
3		1.04		0.95
4			0.45	0.63
5			0.75	0.73
6	0.15	2.18	2.41	1.02
7	0.15	1.00	0.61	1.09
8	0.15			0.74
9	0.15	0.33		1.02
10	0.15	2.16		0.74
11	0.15	1.81		
12		0.96		1.03
13			0.47	0.61
14	0.15	1.31	0.70	
15		0.47	0.61	0.67
16	0.15			1.44
17	0.15	1.06		0.84
18				1.72
19	0.37	0.84		0.81
20		1.07		1.57
21		0.72		0.79
22	0.15	1.58		
23		0.49		0.35
24	0.15	1.34		2.75
25	0.15		2.08	0.85
Mean ± 95% C.I.	**0.17**	**1.26 ± 0.37**	**1.2 ± 0.77**	**1.07 ± 0.26**

($r = 0.850$, $p = 0.004$, Spearman rank-order correlation test) and at 12 months ($r = 0.625$, $p = 0.004$ Spearman rank-order correlation test) post operatively.

The mean post-operative SrCr levels were 22-fold, 23-fold and 21-fold higher at 3, 6 and 12 months post-operative, respectively, than pre-operative levels. The mean post-operative SrCo levels were 8-fold, 7-fold and 6-fold higher at 3, 6 and 12 months post-operative, respectively, than pre-operative levels. The mean post-operative UrCr levels were 9-fold, 10-fold and 14-fold higher at 3, 6 and 12 months post-operative, respectively, than pre-operative levels.

Discussion

There are limited data available on systemic metal concentrations in patients with the old generation metal-on-metal articulating surfaces. Coleman *et al*. [48] reported approximately 3-fold elevation of Cr in whole blood, 11-fold elevations of Co in whole blood and 15-fold elevations of Cr in urine in nine patients with CoCr metal-on-metal total hip replacements in comparison to their preoperative values. No such elevations were observed in patients with metal-on-polyethylene total hip replacements. In three patients for whom longitudinal data were provided, a strong pattern of time dependent Cr and Co concentration increases in blood and urine were observed. Pazzaglia *et al*. [49] reported SrCo values of 0.8 and 0.5 ng/ml, SrCr of 1.8 and 1.5 ng/ml and UrCr of 1.35 and 1.7 ng/ml for two patients with metal-on-metal McKee-Farrar implants that had been *in situ* for 16 years and had acetabular osteolysis. They also presented data on 15 patients with Muller metal-on-polyethylene total hip replacements which had mean SrCo of 0.72 ng/ml, mean SrCr of 1.63 ng/ml and mean UrCr of 1.84 ng/ml. A group of individuals with no implants had a mean SrCo of 0.6 ng/ml, a mean SrCr of 0.5 ng/ml and a mean UrCr of 0.6 ng/ml. They concluded that patients with implants had similar metal levels which were higher than those found in the controls. No differences were found for SrCo. These findings demonstrating no differences between patients with metal-on-metal and metal-on-polyethylene bearing couples are in contrast to our previously reported findings [41]. More recently, Tager [50] reported Co levels in whole blood for two groups of patients who had received CoCr metal on metal McKee-Farrar total hip replacements. In the first group, who had implants *in situ* for 5–9 years, 17 patients were below the detection limit of 20 ng/ml but two patients with loose implants had values of 50 and 120 ng/ml. In the second group of 11 patients with implants *in situ* for 10–14 years, 10 of the 11 patients were at or below a refined detection limit of 10 ng/ml, but one patient had a value of 15 ng/ml. The detection limits presented by Tager are notably higher than presently accepted detection limits reflecting the refinements that have occurred in recent years in the analytical techniques and contamination precautions.

In a retrospective study from our laboratory we reported serum and urine metal levels in a group of patients with McKee-Farrar metal on metal implants *in situ* for over 20 years (range 22–27 years) [41]. The mean SrCr level was 1.28 ng/ml, the mean SrCo level was 0.90 ng/ml and the mean UrCr level was 1.22 ng/ml. All of these levels are lower than what we report here for the modern surface arthroplasty designs at 12 months post-operative, which is still considered within the wear-in period of implants.

With the reintroduction of the new generation metal-on-metal total hip replacements there has been a resurgence of interest in systemic distribution of metal degradation products. Brodner *et al.* [51] in a prospective study with a follow up time of 12 months, reported that all of the 27 metal-on-metal patients (Metasul®), had detectable SrCo values following surgery. These values were significantly higher than in patients with ceramic-on-polyethylene articulating surfaces. Their data show that in the majority of patients, SrCo levels were increased at the 12 month follow up interval compared to the 3 and 6 month intervals. The authors suggested that the wear-in period for these devices may exceed 12 months. The values at 3 and 6 months, presented here for 25 surface arthroplasty patients, are slightly higher than Brodner's values of 1.19 and 0.998 ng/ml, respectively. However, at the 12 month post-operative period the differences are reversed: Brodner's mean value of 2.24 ng/ml is higher than the one in our study (Table IV). This implies that the wear-in period may be shorter for this design of surface arthroplasty than for the total hip replacements studied by Brodner *et al*. However, further follow up is required before definitive conclusions can be drawn.

Schaffer *et al.* [52], studied 76 patients with stable metal-on-metal total hip replacements in a retrospective manner. The patients were grouped according to their post-operative time period of 1, 2 or 3 years. A group of patients about to undergo surgery served as controls. These investigators measured Cr and Co in whole blood and urine. Their data indicate that levels of Co in blood at 2 years were statistically greater than those at 1 year. No differences were found between 1 and 3 years and between 2 and 3 years. In contrast to our data, and to that of Brodner *et al.* [51] they observed no difference between Cr in blood at 1 year post-operative with respect to controls, but did observe differences between the controls and the 2 and 3 year post operative values. They also observed that urinary concentrations for both Co and Cr were increased at all time periods post-operative compared to controls and these differences were statistically significant between the 1 and 2 year post-operative groups. No difference was observed between values at 2 and 3 years post-operative. Although we cannot directly compare our serum values to their whole blood values, we can compare the Cr in urine data. Their mean value of 2.67 ng/ml at 1 year is higher than the value presented here. However, their value was measured from a morning spot urine sample which may tend to have higher metal ion concentrations compared to our urine sample which was collected over a 24-h period.

Gleizes *et al.* [53] also reported on SrCo levels in patients with metal-on-metal articulating surfaces (Metasul®). Their follow-up time ranged from 2.6 to 35 months with a mean of 12.9 months. All of the patients with metal-on-metal implants had higher SrCo values than a group of patients with no implants who had a mean concentration of 0.25 ng/ml. The minimum concentration in patients with implants was 0.51 ng/ml and the maximum was 12.9 ng/ml. They observed that patients who had a follow-up time of greater than 18 months were likely to have higher SrCo values than those whose follow-up time was less than 18 months. They attribute this increase to increased activity after 18 months following surgery.

The only trace metal study regarding metal-on-metal surface arthroplasty is the study published from our laboratory in 1996 [41]. The present values for the current generation of surface arthroplasties are lower than those from an earlier generation of surface arthroplasties of the Wagner and McMinn designs (SrCr = 3.86, UrCr = 5.10, SrCo = 3.77 ng/ml) in patients whose follow up time extended from 2 to 19 months. In a previous longitudinal study from our laboratory [43] using the same analytical techniques, patients with conventional cemented CoCr/ultra high molecular weight polyethylene total hip replacements had mean values at one year of 0.24 ng/ml for SrCo, 0.08 ng/ml for SrCr and 0.15 ng/ml for UrCr. At 36 months these values were slightly higher: 0.27 ng/ml for SrCo, 0.15 ng/ml for SrCr and 0.19 ng/ml for UrCr. The values of these new generation surface arthroplasty patients are 4-fold higher for SrCo, 12-fold higher for SrCr and 12-fold higher for UrCr in comparison to the 36 month concentration of patients with conventional total hip replacements.

The studies presented above, regarding the new generation metal-on-metal designs, indicate that metal levels remain elevated even after the initial wear-in period, usually defined as the first year of service (approximately 1 million cycles). Retrieval studies [40, 54] of the new generation metal-on-metal implants have shown that initial wear rates during the first year of service are in the range of 15–20 μm per component per year. The wear rate significantly decreases to values in the range of 2–5 μm per component per year after the second or third year. There are no published wear data available for the new generation of surface arthroplasties but wear measurements by coordinate measuring machine on short term retrievals of Conserve® Plus components verifies extremely low wear rates (PC, unpublished data). In a hip simulator study of surface arthroplasty components done by McKellop *et al.* [55] they observed similar wear patterns to those of the total hip replacements. The size of the metallic wear particles produced from metal-on-metal total hip replacement implants is considerably smaller (in the range of 15–25 nm) than those of polyethylene wear particles generated from metal-ultra high molecular weight polyethylene total hip replacements [39, 56]. Therefore, for a given volume of wear many more metal particles will be released to the surrounding tissue. This increases the surface area available for corrosion and the subsequent release of metal ions into the system. The increased surface area presented by the wear particles may also contribute to an extended time that metallic ions will be released into the system.

Although the urine chromium levels observed in the surface arthroplasties are elevated, no individual exceeded the Biological Exposure Index (BEI) of 10 μg Cr/g creatinine as adopted by the American Conference of Governmental Industrial Hygienists [57]. The biological exposure index provides a means to assess exposure and health risk to workers and values below the set index indicates no occurrence of adverse affects.

Conclusions

The study presented here is one of the first to present trace metal levels in a prospective manner in patients with metal-on-metal surface arthroplasty of the hip. In this preliminary study the values observed thus far are in the same range as those observed in association with metal-on-metal conventional total hip replacements, which typically have smaller head sizes (range 26–32 mm). However, further follow-up is required before definitive conclusions can be made. While the concentrations presented here are considerably higher than those present in patients with conventional metal-on-polyethylene total hip replacements, no toxic effects have been directly attributed to this observation. From previous studies of long term metal-on-metal McKee-Farrar implants, it seems that these elevated levels will persist for the duration of the implant's lifetime. This is of particular concern in the younger and more active patient and his surgeon where life expectancy after implantation may exceed 30 years. Epidemiological studies [58] concerning populations with orthopedic implants conducted thus far, have predominantly shown that the overall cancer risk is slightly less than that observed in the general population. Some studies however, have also indicated an increase in the incidence of lymphoma and leukemia when individual cancers are examined. At this point in time, there is no cause and effect relationship between cancer and metal-on-metal implants. Further study is needed to fully understand the systemic implications of these persistent elevated metal concentrations.

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