ELEVATED SERUM COBALT WITH METAL-ON-METAL ARTICULATING SURFACES

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We determined serum cobalt levels in 55 patients by atomic absorption spectrophotometry before and after implantation of uncemented total hip arthroplasties. In a randomised, prospective trial 27 wrought Co-28Cr-6Mo-0.2C metal-on-metal articulations were compared with 28 ceramic-on-polyethylene hips which did not contain cobalt. Other sources of iatrogenic cobalt loading were excluded.

The metal-on-metal group produced detectable serum cobalt levels (median 1.1 µg/l after one year) which were significantly different ($p < 0.0001$) from those of the ceramic-on-polyethylene control group (median below detection limit of 0.3 µg/l after one year). Our findings indicate that metal-on-metal bearings generate some systemic release of cobalt.

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Particulate wear debris can initiate aseptic loosening. The presence of aggressive inflammatory tissue has been linked to polyethylene, polymethylmethacrylate and metal particles or to a combination of these.¹⁻⁴ In vitro testing has shown activation of fibroblasts and macrophages⁵ and also cell-mediator release in cell cultures incubated with different types of particle.⁶⁻⁸ Induction of bone resorption has been shown to be a response to cell mediators.^{7,9,10}

To eliminate polyethylene debris and to reduce the total amount of wear, metal-on-metal bearings (Metasul) made of a wrought Co-28Cr-6Mo-0.2C alloy were introduced.¹¹ The linear annual wear of retrieved Metasul prostheses was

only 0.009 mm for the head and 0.006 mm for the acetabular cups¹² compared with 0.08 to 0.25 mm for polyethylene in metal-on-polyethylene or ceramic-on-polyethylene bearings measured radiologically.¹³⁻²⁰

Elevated serum and urine metal levels in patients with orthopaedic implants have been reported²¹ and loose implants were found to generate higher serum metal levels.^{22,23}

Our aim was to determine if metal-on-metal bearings in successful uncemented total hip arthroplasties released enough cobalt to be detectable in the serum.

PATIENTS AND METHODS

In a pilot study, serum samples from patients with metal-on-metal bearings were analysed for metal concentrations. Cobalt and chromium levels were found in some of the samples whereas molybdenum was never detected. Since cobalt represents about two-thirds of the bearing alloy we selected it for further laboratory testing.

Over a period of 17 months all patients ($n = 327$) scheduled for total hip replacement (THR) were subjected to the exclusion criteria of other metallic implants, dental prostheses with cobalt alloys^{24,25} and rheumatoid or osteoarthritis of other major joints. Of the 327 patients, 62 with unilateral osteoarthritis or necrosis of the femoral head satisfied these criteria and consented to be included in the study.

Using a randomisation list, metal-on-metal THRs and similar ceramic-on-polyethylene hips were allocated to these patients (Figs 1 and 2). The cup inlay and the prosthesis head were the only variable parameters. Subsequent exclusion criteria were dislocation, infection, revision surgery and implantation of additional metallic devices. Loss of two consecutive estimations was regarded as loss to follow-up. Seven of the 62 consecutive patients were excluded (dislocation 2, infection and revision surgery 1, hip arthroplasty on the contralateral side 1, screw fixation of femoral head for acetabuloplasty 1, loss to follow-up 2) leaving 55 patients for whom one-year results were available for analysis (Table I).

All classic hip prostheses (stem, forged Ti6Al7Nb alloy; threaded cup, commercially pure titanium) with modular 28 mm diameter heads were implanted without cement.

Blood samples were taken preoperatively and at three

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Fig. 1

Fig. 2

Figure 1 – Alloclassic THR with Metasul metal-on-metal bearing. In the Metasul bearing the metal head articulates with a metal liner which was preinserted industrially into a polyethylene liner. As in the ceramic-on-polyethylene bearings the polyethylene liner is inserted into the threaded titanium cup during surgery. Figure 2 – Alloclassic THR with ceramic-on-polyethylene bearing.

Table I. Details of the 55 patients analysed

	Metal-on-metal	Ceramic-on-polyethylene
Number of patients	27	28
Female:male	18:9	20:8
Mean age in years (range)	58.9 (23 to 80)	61.8 (27 to 87)

and six weeks, three and six months and at one year after surgery, using cobalt-free needles. Serum was stored at -20°C in inert polystyrene tubes until assayed.²⁶ Cobalt levels were determined using electrothermal atomic absorption spectrophotometry (Perkin Elmer 5100-ZL^R, AS-70 autosampler, graphite furnace) with a Zeeman background correction system at a wavelength of 242.5 nm. The detection limit of cobalt in serum by atomic absorption spectrophotometry was $0.3\text{ }\mu\text{g/l}$ in our laboratory. Calibration was done by standard solutions. All samples were analysed in triplicate and single-blinded.

Non-parametric statistical analysis was chosen. All values below the detection limit ($0.3\text{ }\mu\text{g/l}$) were defined to the mean value of $0.15\text{ }\mu\text{g/l}$ for statistical calculations. To assess the serum cobalt levels during the first postoperative year the areas under the curves for each patient were

calculated and compared between the two groups using the Wilcoxon rank-sum test. A value of $p < 0.05$ was considered statistically significant. If one serum sample between two measured cobalt values was missing the value was interpolated.

Clinical evaluation was performed using the Harris hip score.²⁷

RESULTS

Preoperatively, five patients (4 ceramic-on-polyethylene, 1 metal-on-metal) had a detectable serum cobalt level (maximum $0.7\text{ }\mu\text{g/l}$) and 50 had negative levels (Table II).

Postoperatively, all patients in the metal-on-metal group had detectable serum cobalt levels (maximum $11.6\text{ }\mu\text{g/l}$) (Table II). The median serum cobalt level reached $1.0\text{ }\mu\text{g/l}$

Table II. Details of the type of bearing and mean preoperative and postoperative serum cobalt levels ($\mu\text{g/l}$)

Case	Bearing*	Serum cobalt					
		Preop	3 weeks	6 weeks	3 months	6 months	1 year
1	MM	0.15	0.8	0.8	1.9	0.9	1.7
2	CP	0.15	0.15†	0.15	0.15	0.15	0.3
3	CP	0.15	0.15	0.15	0.15	0.15	0.15
4	MM	0.15	0.8	0.15	0.15	0.15	0.8
5	CP	0.15	0.15	0.15	0.15	0.15	0.15
6	MM	0.15	1.7	1.1	0.8	0.15	0.5
7	MM	0.15	1.6	1.1	0.7	1	8
8	CP	0.15	0.15	0.15	0.15	0.3	0.15
9	MM	0.15	0.6	0.465†	0.15	0.15	0.15
10	CP	0.6	0.15	0.15	0.15	0.15	0.15
11	CP	0.15	0.15	0.15	0.15	0.15	0.15
12	CP	0.7	0.15	0.15	0.15	0.15	0.15
13	CP	0.15	0.6	0.465†	0.15	0.15	0.15
14	MM	0.15	0.15	0.9	0.6	1.8	0.7
15	MM	0.15	0.15	0.7	0.15	0.15	0.7
16	CP	0.15	0.15	0.15	0.15	0.15	0.15
17	MM	0.15	0.15	0.15	0.7	2.1	0.5
18	MM	0.15	0.8	0.15	0.15	1	0.7
19	CP	0.15	0.15	0.15	0.15	0.15	0.15
20	MM	0.15	0.15	0.15	0.15	0.5	0.5
21	CP	0.15	0.15†	0.15	0.15†	0.15	0.15
22	CP	0.15	0.15	0.15	0.15	0.3	0.15
23	MM	0.15	0.15	1.7	1.5	1.1	2
24	CP	0.15	0.15†	0.15	0.15	0.15	0.15
25	MM	0.15	0.15	0.15	0.7	0.15	0.15
26	MM	0.15	0.5	0.3	0.5	1.1	1.3
27	MM	0.15	2.9	8.1	11.6	2.4	6.8
28	CP	0.15	0.5	0.15	0.15†	0.15	0.15
29	MM	0.15	0.8	0.9	0.8	1.9	1.1
30	CP	0.15	0.15	0.15	0.15	0.15	0.15
31	CP	0.15	0.15†	0.15	0.15	0.15	0.15
32	MM	0.15	0.6	0.7	1.1	1.1	1
33	CP	0.15	0.15†	0.15	0.15	0.5	0.15
34	MM	0.15	0.7	0.9	0.5	0.4	1
35	CP	0.15	0.15	0.15	0.15	0.15	0.15
36	MM	0.15	1.6	1.66†	1.8	1.4	2.6
37	MM	0.15	0.475†	0.8	0.6	0.8	2.2
38	CP	0.15	0.15	0.15	0.15	0.15	0.15
39	MM	0.15	2.2	2.2†	2.2	1.3	10.4
40	CP	0.6	0.15	0.4	0.4	0.15	0.15
41	MM	0.6	0.9	0.9	0.9	1.4	2.3
42	CP	0.15	0.15	0.15	0.15	0.15	0.15
43	CP	0.15	0.15	0.15	0.15	0.15	0.15
44	MM	0.15	0.3	0.5	1	0.5	4.6
45	MM	0.15	0.7	0.6	0.9	1.6	2.1
46	CP	0.3	0.15	0.4	0.3	0.15	0.15
47	CP	0.15	0.15	0.15†	0.15	0.15	0.15
48	MM	0.15	0.15†	0.15	0.6	0.9	4.4
49	MM	0.15	2.7	1	0.7	1.4	3.1
50	CP	0.15	0.15	0.15	0.15	0.15	0.15
51	CP	0.15	0.15	0.15	0.15	0.15	0.15
52	CP	0.15	0.15	0.15	0.7	0.15	0.15
53	MM	0.15	0.15	0.5	0.3	0.4	0.15
54	MM	0.15	0.6	1.3	1.1	1.2	1.1
55	CP	0.15	0.15†	0.15	0.15	0.15	0.15

* MM, metal-on-metal bearing; CP, ceramic-on-polyethylene bearing

† interpolated value

at the six-month and 1.1 $\mu\text{g/l}$ at the one-year follow-up (Fig. 3).

In 19 of the patients in the ceramic-on-polyethylene group the serum cobalt levels were below the detection limit at all time points after implantation, and nine had measurable serum cobalt levels (maximum 0.7 $\mu\text{g/l}$) after surgery (Table II). The 25%, the 50% (median) and the 75% quartiles of the ceramic-on-polyethylene group were

below the detection limit throughout the entire investigation period (Fig. 3). Fifteen serum samples were not collected and their value was therefore interpolated (Table II).

The Wilcoxon rank-sum test showed a highly significant difference ($p < 0.0001$) in the serum cobalt levels of the two groups.

Clinical evaluation according to the Harris hip score

Fig. 3

Graph of serum cobalt levels. The median (50% quartile) curve of the metal-on-metal group shows a cobalt level of 1.0 µg/l at the six-month follow-up and 1.1 µg/l at the one-year follow-up. The 25%, 50% and the 75% quartiles of the ceramic-on-polyethylene group show levels at 0.15 µg/l below the detection limit at all time points investigated.

showed good function in both groups (metal-on-metal, median 96.9 points; ceramic-on-polyethylene, median 94.5 points).

DISCUSSION

In our patients the Metasul THRs were the only possible sites of cobalt release and were responsible for the increase in the level of serum cobalt.

Reports of the normal plasma and serum cobalt levels in man are extremely variable, between 0 µg/l and 146 µg/l using atomic absorption spectrophotometry and between 0.108 µg/l and 12.2 µg/l using neutron activation analysis.²⁸ Contamination during sample collection and analysis seems to be responsible for this variation. Elinder and Friberg²⁹ reported a level of 0.4 µg/l to be the normal using neutron activation analysis whereas Michel et al³⁰ also using neutron activation analysis reported a normal level of 0.33 µg/l. Sunderman et al²⁶ described a lower mean serum cobalt level of 0.05 µg/l and 0.1 µg/l (using atomic absorption spectrophotometry) respectively, in two unexposed groups, but an upper limit of 0.55 µg/l for the reference range was suggested.

No significant cobalt levels were detected in the preoperative samples of either the metal-on-metal group or the ceramic-on-polyethylene control group; the 75% quartile was below the detection limit of 0.3 µg/l at all time points. We therefore conclude that our patients had not been environmentally or occupationally exposed to cobalt.

There is little information in the literature about cobalt levels and metal-on-metal bearing in THR. Coleman et al²¹ reported an increase in blood cobalt in the first year after the implantation of all-metal cast Co-Cr-Mo metal-on-metal prostheses in nine patients (preoperative mean value of 0.6 µg/l, postoperative mean value 6.5 µg/l) which dif-

fered from metal-on-polyethylene prostheses (preoperative mean value 0.7 µg/l, postoperative mean value 0.3 µg/l). In our study we measured serum cobalt which may account for the lower cobalt levels when compared with the results of Coleman et al on whole blood.

Lower plasma cobalt levels were found in two patients (0.8 and 0.5 µg/l, respectively) with successful McKee-Farrar cast metal-on-metal prostheses 16 years after implantation.³¹ These levels were similar to those in 15 patients with successful Müller metal-on-polyethylene prostheses after 7 to 15 years (mean 0.72 µg/l) and in subjects of a control group without metal exposure (mean 0.6 µg/l). This finding of no difference in cobalt levels irrespective of the type of the bearing contrasts with our data. Furthermore, in all-metal prostheses of the McKee-Farrar type release may be from different sites.

Wear at the bearing surfaces¹² seems to be responsible for generating release, but corrosion of the implant materials^{25,32} or of the wear particles³³ may also contribute to release³⁴⁻³⁶ in conjunction with wear. In addition, corrosion^{37,38} at the modular head and neck interface may increase serum cobalt.³⁹ Jacobs et al³⁹ correlated the extent of corrosion in mixed-alloy modular metal-on-polyethylene THRs with the serum cobalt levels in 15 patients. Four out of ten patients with moderate or severe corrosion, however, and three out of five patients with mild or negligible corrosion had other metallic implants. The findings therefore were inconclusive.

The early increase in cobalt levels three weeks after the operation in relatively inactive patients seems to be due to a wearing-in phenomenon. We do not know if a decrease in wear, after an initial period of accelerated wear,^{40,41} will result in decreased levels.

A concomitant chromium release and therefore elevated serum chromium levels^{21,23,42} must also be assumed in our

patients. Metal release to the periprosthetic tissues is well known.^{2,4,22,43-46} Disseminated metal particles have been shown to accumulate in regional lymph nodes causing sinus histiocytosis,⁴⁷ necrosis⁴⁸ and cytokine production.⁴⁹ Furthermore, accumulation in distant organs^{30,48,50,51} has also been clearly demonstrated.

Toxic serum levels of cobalt after release from implants have not been observed^{29,52} nor is there any evidence of cobalt-associated pathology, such as cardiomyopathy^{53,54} or pneumopathy.⁵⁵ Nevertheless, the possible long-term biological effects of elevated serum metal levels in man require investigation.

Friedman et al⁵⁶ requested more information on the performance of biomaterials in vivo since much of our knowledge about the function of these in man has been gained by retrieving and analysing failed implants. Analysis of serum cobalt may be used as a clinical parameter for the study of the performance of a metal-on-metal bearing.

Conclusion. Our findings show that metal-on-metal bearings (Metasul) generate detectable serum cobalt levels in patients with symptom-free uncemented THRs. They indicate a median serum cobalt level of 1.0 µg/l at the six-month and of 1.1 µg/l at the one-year follow-up.

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