

# Metal ions in body fluids after arthroplasty

We measured levels of metal ions in urine and plasma of 17 patients 7-15 years after they had a Co-Cr-Mo alloy total hip replacement. They had higher levels of cobalt and chromium than controls. No case of skin sensitivity to the investigated metals was observed. The values of cobalt and chromium in plasma and urine were considerably lower than in professionally exposed groups and do not represent a toxic hazard for the patients.

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As observed both experimentally and clinically, small quantities of metal ions are released from the surface of Co-Cr-Mo alloy implants (Laing et al. 1959, Emnéus et al. 1960, Ferguson et al. 1960, 1962, Coleman et al. 1973, Lord et al. 1979, Dobbs & Minski 1980, Jorgensen et al. 1983), and these quantities may increase dramatically in cases of failed prostheses (Evans et al. 1974, Jones et al. 1975). The importance of metal release from the implant is due to the risk of toxicity and of sensitivity to metals as a possible cause of loosening (Evans et al. 1974, Elves et al. 1975, Langlais et al. 1980, Uchida et al. 1980) and of carcinogenicity (Oppenheimer et al. 1956, Heath et al. 1971, Kazantzis 1981, Norseth 1981). Few long-term studies have been performed on the levels of metal ions in organic fluids of patients with orthopedic implants (Brown et al. 1977, Pazzaglia et al. 1983).

We have assessed the levels of metal ions in patients with Co-Cr-Mo alloy total hip replacements after 7-15 years.

## Patients and methods

We studied 17 patients who underwent a total hip arthroplasty 7-15 years ago at Istituto Ortopedico Rizzoli in Bologna and in whom the operation was still considered successful. In 15 patients a Mueller Co-Cr-Mo alloy prosthesis was applied articulating

against a RCH 1000 polyethylene socket, and in 2 patients a McKee-Farrar metal-to-metal prosthesis was used. The average age was 68 (45-80) years.

The patients' occupations during the past 30 years and the presence of industries near the place of residence were carefully investigated. Alcohol and tobacco consumption and drugs taken in the last 2 years were recorded. The patients were examined for evidence of hemophilia, thalassemia, Wilson's disease, diabetes, and liver, kidney, and heart diseases.

For every patient a test tube of whole blood was refrigerated at +5° C, whereas another was centrifuged at about 2,500 rpm at room temperature, and the plasma pipetted and stored at -20° C until 6 hours before beginning the analysis. Urine samples were taken using plastic containers washed with a 10 per cent nitric acid and water solution and then repeatedly with bidistilled water.

Analytical determinations were performed with two Perkin Elmer atomic absorption spectrophotometers, models 5000 and 603, equipped with HGA 500 and HGA 76b, respectively.

The determination of cobalt in urine was improved using a digestion procedure (wet ashing with nitric and sulfuric acid). The ashed solution was adjusted to pH 3.5 and the cobalt was extracted with ammonium pyrrolidine dithiocarbamate/methyl-isobutylketone (Ichikawa et al. 1985). Plasma samples were dried in a low temperature asher and resolved with diluted nitric acid. A microaliquot of the organic layer (methyl-iso-butylketone) or 1N HNO<sub>3</sub> was analyzed by electrothermal atomic absorption spectrometry.

Chromium determination in plasma and urine was performed following the method of Guthrie et al. (1978), partially modified for the utilized equipment. Manganese determination in blood and urine was performed using both the method of Ross & Gonzales (1974) and the extractive procedure with sodium diethylthiocarbamate/methyl-iso-buthylketon (Minoia & Cavalleri 1982). The determination of molybdenum in plasma and urine was performed using the method of Baert et al. (1976).

Accuracy, precision, and detection limits of the methods employed are reported in Table 1.

Skin sensitivity to the alloy metals was examined using epicutaneous tests with the following haptens: a 2 per cent solution of  $\text{CoCl}_2$ , a 0.5 per cent solution of  $\text{K}_2\text{Cr}_2\text{O}_7$ , and a 2 per cent solution of  $2\text{MnCl}_2$ . A trained dermatologist read the skin test after 48 h.

The control group consisted of apparently healthy persons of both sexes, with no history of prostheses or other metallic implants. They were all residents of Lombardia and had not been professionally exposed to the metals tested. Plasma and urine samples were collected from April 1982 until November 1983, with the same procedures formerly reported; only individuals with normal values of glucose and plasma lipids were included.

The Student's *t* test was used for the statistical calculations.

## Results

Because radiotransparent cement was used, the bone-cement interface was difficult to assess. Fractures of the cement could not be seen. However, in 10 patients osteolysis of the bone around cement of the acetabulum, of the femur, or both were evident, and in 6 patients re-

Table 1. Accuracy, precision and detection limits of the methods employed

Element	Biological matrix	Detection limit (ug/l)	Precision <sup>a</sup> CV % (in the series)	Recovery %	No of patients
Co	Urine	0.05	16.2	88.9	15
Co	plasma	0.05	15.8	94.7	18
Cr	urine	0.02	9.7	89.9	12
Cr	plasma	0.03	7.8	95.1	13
Mo	urine	0.8	20.8	92.7	14
Mo	plasma	0.8	24.2	96.1	14
Mn	urine	0.02	8.7	94.8	16
Mn	blood	0.02	8.2	94.7	15

<sup>a</sup> The data refer to physiological levels of the metal. CV = Coefficient of variation.

Table 2. Radiographic evaluation of Co-Cr-Mo alloy prostheses

Case	Time (yr)	Osteolysis		Calcar resorption
		Acetabulum	Femur	
1	9	-	-	-
2	8	-	-	+
3	9	-	+	-
4	7	+	+	+
5	10	-	+	-
6	9	-	-	-
7	8	-	-	-
8	8	+	-	+
9	8	-	-	-
10	8	-	+	-
11	15	-	-	+
12	10	-	-	+
13	13	-	+	+
14	8	-	+	-
15	9	+	-	-
16	16	+	-	-
17	16	+	-	-

Cases 1-15 Mueller prostheses, Cases 16 and 17 McKee-Farrar prostheses.

Table 3. Cobalt, chromium, molybdenum and manganese levels in biological fluids of 15 patients with Co-Cr-Mo alloy Mueller prosthesis, of two patients with metal on metal McKee-Farrar prosthesis and controls. Mean (SD)  $\mu\text{g/l}$ . P-values refer to comparison with controls

Metal and biological matrix <sup>a</sup>	Control	No of patients	Mueller	McKee-Farrar ( $\mu\text{g/l}$ )	P-value
$\text{Co}_{\text{pl}}$	0.6 (0.3)	28	0.72 (0.58)	0.8 0.5	n.s.
$\text{Co}_{\text{u}}$	0.5 (0.2)	36	0.86 (0.37)	1.05 0.4	<0.01
$\text{Cr}_{\text{pl}}$	0.5 (0.1)	310	1.63 (0.45)	1.80 1.5	<0.01
$\text{Cr}_{\text{u}}$	0.6 (0.2)	70	1.84 (0.54)	1.35 1.7	<0.01
$\text{Mo}_{\text{pl}}$	<1 $\gamma\text{/l}$	28	<1 $\gamma\text{/l}$	<1 $\gamma\text{/l}$	
$\text{Mo}_{\text{u}}$	<1 $\gamma\text{/l}$	28	<1 $\gamma\text{/l}$	1.1 0.85	
$\text{Mn}_{\text{b}}$	9.0 (0.1)	20	6.99 (0.97)	7.0 6.0	n.s.
$\text{Mn}_{\text{u}}$	1.2 (0.4)	136	1.26 (0.6)	0.96 0.75	n.s.

<sup>a</sup>pl = plasma b = blood u = urine

sorption of the calcar was also observed (Table 2).

Increased levels of Co and Cr in urine and of Cr in plasma were found among the patients (Table 3). Metal ion values in plasma and urine of the two McKee-Farrar, metal on metal prostheses were in the same range as for metal plastic prostheses. There was no correlation between prostheses with osteolysis around the cement and the levels of metal ions in plasma and urine.

Skin sensitivity tests to Co, Cr, and Mn were negative in 15 patients; 2 did not return for the control appointment.

## Discussion

Our results are not unexpected because cobalt and chromium are the major constituents of the Co-Cr-Mo alloy (approximately 65 and 30 per cent, respectively); by contrast, molybdenum and manganese represent only 5 and 1 per cent.

The ratio of cobalt to chromium in the parent alloy is approximately 2:1, whereas the ratio of soluble ion levels in plasma and urine was inverted. This observation accords with Evans et al. (1979); in 8 of 10 cases, they found higher quantities of chromium than cobalt in the tissue adjacent to the prosthesis. The same results were obtained by Dobbs & Minsky (1980) in the joint fluid, joint capsule, granuloma, and bone of a necropsy case where two Co-Cr-Mo alloy hip prostheses had been applied. In the same paper chromium concentration was reported to be higher than cobalt in kidney, liver, spleen, and hair.

Rae (1979) observed that chromium has a lower solubility from the alloy than cobalt. On the contrary, our study showed higher levels of soluble chromium in biological fluids. Soluble metals form complexes with proteins and small molecular components of biological fluids (Heath et al. 1969, Maroudas 1973); therefore, it is likely that the more soluble cobalt ions form complexes that are more easily excreted.

Metal-ion release implies contact of the metal surface with interstitial fluids. If the technic of cementation is correct, all the stem should avoid such contact. However, from our experience, some sort of fluid circulation must occur in the stem-cement interface, for we have often observed a thin layer of fibrous tissue in firmly bound prostheses, also when no subsidence of the stem or fracture of the cement was present.

The urine chromium levels were considerably lower than in professionally exposed groups, where the urinary excretion of chromium is usually used for biological monitoring of workers exposed to water-soluble chromium. The observed levels of metals among our patients therefore should not represent a toxic hazard.

In patients, chromium is released from the implant surface or from particles formed by

wear, and it seems likely that it consists almost exclusively of metallic or trivalent chromium because no possibility exists in vivo for oxidation to hexavalent chromium ions.

Tumor induction has been observed in industrial workers after exposure to hexavalent chromium, but not to the trivalent ion.

In orthopedic practice, two patients have been reported in whom tumors developed at the site of a metal plate implanted 30 years before (Dube & Fisher 1972, McDougall 1956); in both cases the stainless steel plate and the screws showed extensive corrosion, and in one of them an important macrophagic reaction was demonstrated around the implant (Dube & Fisher 1972). A third patient was reported to have developed an osteosarcoma at the site of a plate after only 3 years, but the types of material involved were not mentioned (Delgado 1958).

Quite recently, a malignant fibrous histiocytoma and an osteosarcoma have been reported for the first time at the site of two all-metal Co-Cr-Mo alloy prostheses after 4 and 5 years (Penman & Ring 1984, Swann 1984).

Because of the large number of hip replacements performed to date, the few observations of tumors at the site of a prosthesis may be coincidental; in none of them has definite evidence of tumor induction by metal ions been presented.

Skin sensitivity to Co-Cr-Mo alloy metals, especially cobalt, has been considered to be a possible test for demonstrating allergic reactions to the constituents of the implant, which eventually may lead to loosening (Benson et al. 1975, Evans et al. 1975, Uchida et al. 1980). Skin sensitivity was not observed in our patients, not even after long-term exposure to the alloy metals.

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