Changes in serum chromium levels over 12 years after Metasul metal-on-metal total hip arthroplasty

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ABSTRACT

We reported the longitudinal changes in serum chromium levels over a minimum of 7 years postoperatively in five men and 25 women with a mean age of 60.3 years after primary unilateral total hip arthroplasty with a Metasul metal-on-metal articulation. The serum chromium ion level showed little variation (0.6–1.2 µg/L) from 2 to 12 years postoperatively in 16/30 patients after unilateral primary Metasul metal-on-metal total hip arthroplasty. On the other hand, the serum chromium level stayed high or showed gradual elevation in 8/30 patients, even though they had well-fixed and well-functioning prostheses.

1. Introduction

There has been concern regarding the potential effects of prolonged exposure to increased levels of metal ions after metal-on-metal resurfacing arthroplasty and metal-on-metal total hip arthroplasty, including possible hypersensitivity, carcinogenicity, and adverse effects on the fetus in pregnant women. Recent studies have also shown an increase in other metal-related problems, including aseptic lymphocyte-dominated vasculitis-associated lesions and pseudotumor formation. Therefore, it seems important to determine the changes in blood metal ion levels after implantation of metal-on-metal prostheses.

We previously reported on the longitudinal changes in serum chromium levels for a minimum of 7 years postoperatively in 44 patients who had undergone primary unilateral total hip arthroplasty using a Metasul metal-on-metal articulation (Sulzer Medica, subsequently Zimmer, Winterthur, Switzerland).¹ In that study, we found that while the serum chromium concentration was ≤ 1.0 µg/L throughout 7 years after Metasul metal-on-metal total hip arthroplasty, serum chromium levels did not fall postoperatively in 25% of patients and remained elevated even 7 years after implantation in most of them.

In the present study, we continued prospective longitudinal investigation of serum chromium concentrations for a minimum of 12 years after surgery in the same group of patients with well-functioning unilateral Metasul metal-on-metal hip articulations.

2. Patients and methods

Between November 1997 and April 2001, 110 consecutive patients (116 hips) underwent primary total hip arthroplasty with the Metasul metal-on-metal prosthesis (Zimmer GmbH, Winterthur, Switzerland). Blood samples were collected from each patient every 6 months after surgery to investigate longitudinal changes in the serum chromium level after metal-on-metal total hip arthroplasty.

All of the prostheses were implanted without cement. The femoral head and stem were the same in all patients. The femoral head was made of Co-Cr alloy (Protasul-21 WF) and was 28 mm in diameter, while the stem was a Natural Hip Stem made of titanium alloy (Ti6Al4V) with a proximal circumferential porous coating. Two acetabular components were used, which were the Wagner standard cup and the APR cup. In Japan in those days, the minimum diameter of the APR cup is 49 mm, and the Wagner standard cup was implanted when a smaller diameter was required. Accordingly, these components were selected according to the outer diameter of the acetabulum, with the Wagner standard cup being used when it was less than 49 mm and the APR cup being used when it was 49 mm or more. Both cups had a 2.4 mm thick articular surface of CoCr alloy (Protasul-21 WF, Zimmer) molded onto ultra-high molecular weight polyethylene that was backed with titanium (Table 1).

Blood samples were collected and handled carefully to avoid contamination with metal ions, with the instruments used for blood collection being pre-tested to ensure that they were free of contamination.

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Table 1
Patients demographics.

Gender	Male	5
	Female	25
Age	Mean (range)	60.3 (49–77)
Initial diagnosis	Osteoarthritis	29
	Osteonecrosis	1
	Rheumatoid Arthritis	0
	Mean (range) (Y)	14.4 (12–17)
Body weight	Male (mean $\pm$ S.D.)	64.4 $\pm$ 6.3
	Female (mean $\pm$ S.D.)	53.3 $\pm$ 8.7
BMI	Male (mean $\pm$ S.D.)	24.5 $\pm$ 1.8
	Female (mean $\pm$ S.D.)	23.9 $\pm$ 4.2
Implant		
	Shell	APR 13
		Wagner standard cup 17
	Stem	Natural hip stem 30
Lateral cup angle	Mean $\pm$ S.D. (range)	45.2 $\pm$ 5.9 (35–55)

A disposable intravenous cannula was used. Once the cannula had entered an appropriate vein, we immediately withdrew the stainless steel stylet and left the outer plastic tube in situ. The initial 10 mL of blood was discarded to exclude possible contamination by debris in the cannula, after which a further 10 mL of blood was withdrawn and used for analysis. The serum concentration of chromium was measured by atomic absorption spectrophotometry at Mitsubishi Kagaku Biochemistry Laboratories (Tokyo, Japan). All samples were tested twice and the detection limit was 0.2 $\mu\text{g/L}$.

Statistical analysis was performed with StatView Ver. 5.0 software for Macintosh (SAS Institute Inc., North Carolina). Fisher's PLSD test was used to determine the significance of differences in the mean serum chromium level from 1 to 12 years postoperatively. All serum chromium values below the detection limit were set as the mean value of 0.1 $\mu\text{g/L}$ for statistical calculations. A p value < 0.05 was considered to indicate statistical significance.

3. Results

Of the original 110 patients, 6 patients who underwent bilateral metal-on-metal total hip arthroplasty and 26 patients who already had metal-on-polyethylene total hip arthroplasty of the contralateral hip joint were excluded from the present study. In addition, the following patients were excluded because of events during the 12-year follow-up period: 20 patients who were lost to follow-up (referred back to the original hospital or moved to another area), 19 patients who underwent revision surgery due to aseptic loosening of the acetabular component (18 had a Wagner standard cup and 1 had an APR cup), and 9 patients who died of unrelated causes. The remaining 30 patients were investigated.

The 30 patients included 5 men and 25 women, with a mean age at operation of 60.3 years (range: 49–77 years). Twenty-nine patients had osteoarthritis of the hip due to acetabular dysplasia and one had osteonecrosis of the femoral head. The mean height, body weight and BMI of the men and women was 162 ± 2.5 cm, 64.4 ± 6.3 kg and 24.5 ± 1.8 versus 149.6 ± 4.9 cm, 53.3 ± 8.7 kg, and 23.9 ± 4.2 , respectively (Table 1). None of the patients had other metallic implants, dental prostheses containing chromium alloy, or exposure to metal during daily activities. The level of activity of all 30 patients was similar, i.e., all of them could walk more than six blocks without assistance and could ascend/descend stairs. None of the patients performed strenuous physical labor or contact sports. None of the patients had any symptoms or signs of local toxicity, hypersensitivity, or malignancy. Radiography showed no bone loss or loosening of the prosthesis. Also, none of the patients had renal dysfunction either preoperatively or postoperatively.

A Wagner standard cup was used in 17 patients and 13 patients had an APR cup. All of the prostheses functioned well, as determined by a

Fig. 1. Chronological change of the mean serum chromium level.

good or excellent Harris Hip Score, and there was no radiographic evidence of loosening, osteolysis, or infection during follow-up. There was no significant variation of the lateral cup angle among the 30 patients and the mean (mean $\pm$ SD) lateral cup angle at implantation was 45.2 ± 5.9 (range: 35–55) degrees (Table 1).

In the 30 patients, the mean $\pm$ SD serum chromium level ($\mu\text{g/L}$) was as follows: 0.68 ± 0.65 (range: 0.2–2.7) at 6 months, 0.92 ± 0.51 (range: 0.2–2.1) at 1 yr, 1.44 ± 0.87 (range: 0.1–3.5) at 2 yrs, 1.76 ± 1.52 (range: 0.1–6.6) at 3 yrs, 1.53 ± 1.24 (range: 0.3–5.6) at 4 yrs, 1.31 ± 0.73 (range: 0.4–3.3) at 5 yrs, 1.16 ± 0.73 (range: 0.1–3.1) at 6 yrs, 1.43 ± 0.92 (range: 0.4–4.2) at 7 yrs, 1.29 ± 1.16 (range: 0.1–6.2) at 8 yrs, 1.26 ± 1.04 (range: 0.1–4.3) at 9 yrs, 1.36 ± 1.13 (range: 0.1–5.5) at 10 yrs, 1.26 ± 1.40 (range: 0.1–7.1) at 11 yrs, and 1.19 ± 1.18 (range: 0.1–5.9) at 12 yrs. Further monitoring was continued in most of the patients, with the mean serum chromium level being 1.38 ± 1.33 (range: 0.1–5.6) in 28 patients at 13 yrs, 1.42 ± 1.58 (range: 0.1–7.9) in 24 patients at 14 yrs, and 1.09 ± 0.83 (range: 0.1–3.1) in 16 patients at 15 yrs (Fig. 1). The mean serum chromium level increased between 6 months and 3 years after implantation, and there were significant differences in the mean serum chromium level between 6 months and 2 to 12 years postoperatively (all $p < 0.05$). There was a decrease in the mean serum chromium level between 3 and 6 years after surgery, but serum chromium was stable after 7 years and there was no significant differences in the mean level from 7 to 12 years postoperatively (approximately 1.3 $\mu\text{g/L}$ in each year). There was no difference in the mean serum chromium level between the patients with a Wagner standard cup and those with an APR cup.

Based on the pattern of changes in the serum chromium level over time, the 30 patients were classified into four groups. In group I (3 men aged 59–63 years and 13 women aged 49–65 years), serum chromium was low throughout the 12-year follow-up period (always approximately 0.9 $\mu\text{g/L}$). In group II (4 women aged 70–77 years), serum chromium was 2 $\mu\text{g/L}$ or higher from 2 to 12 years postoperatively. In group III, (a 55-year-old man and 5 women aged 54–65 years), the serum chromium decreased from 3 to 7 years postoperatively and then was around the same level as in group I from 7 to 12 years. In group IV, (a 62-year-old man and 3 women aged 58–70 years), there was a gradual increase in serum chromium levels over time after 7 years postoperatively (Fig. 2). Individual chronological changes in serum chromium in the patients from groups II, III, and IV are displayed in Fig. 3. One patient (a woman who was 70 years old at operation) showed a serum chromium level $> 7 \mu\text{g/L}$ at 11 and 14 years postoperatively (7.1 and 7.9 $\mu\text{g/L}$, respectively). In this patient, the serum chromium level increased from 0.4 $\mu\text{g/L}$ to 6.6 $\mu\text{g/L}$ during the period from 1 to 3 years after surgery. Then the chromium level decreased from 6.6 $\mu\text{g/L}$ to 2.6 $\mu\text{g/L}$ between 3 and 5 years postoperatively, but rose again to 6.2 $\mu\text{g/L}$ by 8 years and then stayed in the range from 4 to 8 $\mu\text{g/L}$ until 14 years postoperatively. This patient has had no symptoms or findings

Fig. 2. Chronological change of the serum chromium level according to classified into four patterns.

on examination or X-ray, and she has been observed without revision surgery.

4. Discussion

Many concerns remain regarding the consequences of prolonged exposure to metal ions, such as hypersensitivity, carcinogenicity, and effects on the fetus in pregnant women. There have been reports of patients with metal hip prostheses who developed serious symptoms, including neurological symptoms (auditory impairment, visual impairment, peripheral neuropathy, and poor concentration), cardiomyopathy, and hypothyroidism. Metal debris that enter the periprosthetic tissues can trigger local inflammatory reactions and provoke the formation of soft tissue masses and fluid collections. Such local reactions can lead to tissue necrosis and osteolysis, ultimately resulting in

early failure of the prosthesis and the need for revision surgery. Biological responses to metal particles have been characterized as adverse reactions to metal debris (ARMD), aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL), and formation of pseudotumors. In most cases, these conditions are thought to represent a toxic reaction to the accumulation of metal particles.

A wide variety of metal-on-metal articulations are available, with differences in the metal alloy, size, design, use of polyethylene, and manufacturing method. The surface quality and hardness of cobalt-chromium alloy bearings depend on the carbon content of the alloy and on the metallurgical techniques used in production. Several nonclinical studies have shown that high-carbon cobalt-chromium alloys demonstrate greater wear resistance than low-carbon alloys.^{2,3} Aseptic loosening seems to be the main reason for failure of metal-on-metal articulations made from low-carbon wrought CoCr alloys. Milosev et al⁴ and Korolessis et al⁵ reported a revised failure rate of 4% due to aseptic loosening after follow-up for a mean of 7 years and 5–9 years, respectively. For a metal-on-metal articulation with the combination of a high-carbon cast cup and a low-carbon wrought CoCr head, Park et al⁶ reported a high rate of periprosthetic osteolysis affecting the great trochanter (5.9%).

In such circumstances, excellent results have been reported for the Metasul articulation system composed of high-carbon wrought CoCr alloy. The survival rates reported by Eswaramoorthy et al⁷, with aseptic loosening as the endpoint, were 99% for the cup and 100% for the stem. Filippo et al⁸ studied the survival rate of metal-on-metal articulations, and reported 99% survival at 14 years with revision for metal debris-related aseptic loosening as the endpoint. On the other hand, some problems with the Metasul articulation have also been reported. Dastane et al⁹ reported that 8 of 119 hips (7%) required revision (2 for recurrent dislocation, 2 for aseptic loosening, and 4 for dissociation) by a mean of 13 years postoperatively in patients receiving

Fig. 3. (A) Chronological change of the serum chromium level whose belonging to Group II. (B) Chronological change of the serum chromium level whose belonging to Group III. (C) Chronological change of the serum chromium level whose belonging to Group IV.

a Metasul articulation with a 28-mm head. The reason for dissociation was suggested to be high frictional torque at the articulation surfaces or intolerance to impingement. We also reported 2 cases of dissociation of a Metasul articulation (28-mm head and APR cup) due to breakage of the locking mechanism between liner and shell.¹⁰

The blood levels of metal ions seem to show considerable variation after metal-on-metal total hip arthroplasty. Regarding the short- to mid-term outcome, Hasegawa et al.¹¹ studied asymptomatic patients with well-functioning metal-on-metal implants (Cormet cup and CTi II stem) over a 2-year period, and reported that cobalt and chromium ion levels reached a steady state at 1 year, typically around 2 µg/L. Also, Bernstein et al.¹² reported that the median whole blood chromium level reached a maximum of 0.75 µg/L after 5 years and then decreased to 0.65 µg/L after 7 years in 82 patients (87 hips) who underwent Metasul metal-on-metal total hip arthroplasty. Moreover, Moroni et al.¹³ reported that metal ion levels did not increase again after falling or reaching a plateau. Among long-term studies, Grubl et al.¹⁴ reported that the median chromium ion level was 0.95 µg/L in 22 patients after a minimum follow-up period of 10 years. In addition, Malek et al.¹⁵ reported a mean final plasma chromium level of 3.6 µg/L in 67 patients with a median age and mean follow-up period of 66 years and 13 years, respectively. In our study, we found that the serum chromium ion level showed little variation (0.6–1.2 µg/L) from 2 to 12 years postoperatively in 16/30 patients after unilateral primary Metasul metal-on-metal total hip arthroplasty. On the other hand, the serum chromium level stayed high or showed gradual elevation in 8/30 patients, even though they had well-fixed and well-functioning prostheses. These results indicate that the serum chromium concentration continues to change in some patients after metal-on-metal total hip arthroplasty.

Though most authors agree that cobalt and chromium concentrations should not be used in isolation to assess patients with metal-on-metal prostheses and must be considered together with symptoms and imaging findings,¹⁶ the Medicines and Healthcare Products Regulatory Agency of the United Kingdom has suggested that patients with cobalt or chromium ion levels above 7 µg/L should be investigated further and ion measurements should be repeated as part of closer follow-up. Malek et al.¹⁵ reported plasma chromium levels > 7 µg/L in 4 asymptomatic patients. One of our patients showed a serum chromium level > 7 µg/L at 11 and 14 years postoperatively; hence, careful follow-up and monitoring might be needed although she has no symptoms.

In conclusion, the serum chromium concentration was ≤ 1.2 µg/L throughout 12 years of postoperative follow-up in approximately half of our patients after Metasul metal-on-metal total hip arthroplasty, but serum chromium stayed high or showed gradual elevation in about one-fourth of our patients. Accordingly, we should recognize that the serum

chromium level can remain high or show gradual elevation after metal-on-metal arthroplasty and careful follow-up and monitoring might be needed to detect metal toxicity in such patients.

Conflict of interest

None

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