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Concentration of Metal Elements in the Blood and Urine in the Patients with Cementless Total Knee Arthroplasty

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Liu, T.-K., Liu, S.-H., Chang, C.-H. and Yang, R.-S. *Concentration of Metal Elements in the Blood and Urine in the Patients with Cementless Total Knee Arthroplasty.* Tohoku J. Exp. Med., 1998, **185** (4), 253-262. —— Titanium (Ti), cobalt (Co) and chromium (Cr) element concentrations in the whole blood and urine specimen in 40 patients with cementless total knee arthroplasty were determined by the electrothermal atomic absorption spectrophotometry. Their ages ranged from 55 to 78 years (mean, 65 years). Twenty of them had loosening of prosthesis and underwent revision surgery, including 4 subjects with Ti-6Al-4V alloy prosthesis and 16 subjects with Co-Cr-Mo alloy prosthesis. The other 20 patients had well-functioning stable prosthesis, including 5 subjects with Ti-6Al-4V alloy prosthesis and 15 subjects with Co-Cr-Mo alloy prosthesis. The mean duration of prostheses implantation in patients with loosened or well-functioning prostheses were 6.5 and 4.0 years, respectively. The control group consisted of 20 age-matched normal subjects who did not undergo any metal implant surgery. Analysis of variance showed that the metal element concentrations in the whole blood, either Co, Cr or Ti, was statistically higher in the patients with loosened prosthesis than the other two groups. However, the metal element concentrations in the urine did not show any difference. The linear regression analysis showed a moderate positive relationship between the metal element concentrations, either Co or Cr elements, in whole blood and urine only in the patients with loosened prostheses. In conclusion, elevated concentration of metal elements may indicate a loosening of prosthesis while the clinical significance of the metal element concentration in the urine needs further investigation. ——— metal elements; cementless; total knee arthroplasty; blood; urine

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With the increasing number of severe arthritic patients and advances of the reconstructive techniques and biomaterial science, total joint arthroplasty has become a common procedure in the orthopaedic practice. Despite the successful clinical outcomes, there existed a few post-operative complications, including infection, dislocation, loosening of the prosthesis, fractures of the implant or femoral shaft, and regional bone osteolysis, etc. Loosening of the implant remains a difficult clinical challenge to the orthopaedic surgeons. The pathogenesis of the loosening is not well understood.

Recent studies showed that periprosthetic bone resorption (regional osteolysis) may be one of the main underlying cause and are related to the wear particles (Gruen et al. 1979; Tetlebaum and Kahn 1980; Anderson et al. 1986; Zaidi et al. 1987; Agins et al. 1988; Engh and Bobyn 1988; Horowitz et al. 1988, 1993; Baron 1989; Lombardi et al. 1989; Bobyn et al. 1990, 1992; Dorr et al. 1990; Santavirta et al. 1990, 1993; Harris 1991; Callaghan 1993; Maloney and Smith 1995). The release of metal debris was supposed to be an important underlying mechanism (Agins et al. 1988; Dorr et al. 1990; Salvati et al. 1993; Maloney and Smith 1995). The possible mechanism of bone resorption may be related to the high activity of the osteoclasts caused by the phagocytosed wear debris (Tetlebaum and Kahn 1980; Anderson et al. 1986; Zaidi et al. 1987; Baron 1989; Maloney and Smith 1995).

The joint replacement operation with metal implant would increase the chance of the exposure to the metal elements which will increase the concentration of the metal elements in the body fluids (Dobbs and Minski 1980; Black et al. 1983; Pazzaglia et al. 1986; Stulberg et al. 1987; Agins et al. 1988; Lombardi et al. 1989; Sunderman et al. 1989; Dorr et al. 1990; Harris 1991; Lewis et al. 1991; Michel et al. 1991; Brien et al. 1992; Langkamer et al. 1992; Salvati et al. 1993). The advance of the cementless prosthesis would increase of contact surface due to the porous coating surface and enhance corrosion rate. The increased release of metal elements into local tissue and systemic circulation would cause the deleterious effects of bone metabolism (Gruen et al. 1979; Agins et al. 1988; Engh and Bobyn 1988; Horowitz et al. 1988, 1993; Bobyn et al. 1990, 1992; Santavirta et al. 1990, 1993; Harris 1991; Callaghan 1993). Therefore, measurement of postoperative change of the metal element concentrations in the serum, joint fluid and urine may help us understand the regional bone metabolism after total joint arthroplasty.

In this study we measured the metal elements in the whole blood and urine specimens with atomic absorption spectrophotometry. This result would help us understand the effects of the total joint replacement on the systemic metabolic changes. The hypothesis to be tested is that the metal element concentrations would be higher in the patients with loosened prostheses. The purpose of the present study was to evaluate the change of metal element concentrations in the body fluids of patients with stable and loosened prostheses.

Materials and Methods

Twenty patients with loosened noncemented total knee arthroplasty were included in the present study. The loosening of prosthesis has been confirmed by the radiographic evidence of radiolucency around the prosthesis as well as the extent of in situ motion during the revision surgery. There were 8 males and 12 females with the ages ranging from 55 to 78 years (mean, 65 years). The loosened prostheses included 4 subjects with Ti-6Al-4V alloy prosthesis (MG-I, Zimmer Co., Warsaw, IN, USA) and 16 subjects with Co-Cr-Mo alloy prosthesis (9 PCA [Howmedica Co., Rutherford, NJ, USA], 4 Tricon [Richard Co., Memphis, TN, USA], and 3 LCS [Depuy Co., Warsaw, IN, USA]). The latter prostheses are made of Co: 60–64%, Cr: 27–30% and Mo: 5–7%, and Ni, Mg, Fe: <1%. All patients with loosened prostheses underwent revision of the prosthesis. Metallosis or prosthesis wear was noted in the revision operation. The duration of the implant ranged from 2.2 to 9.4 years (mean, 6.5 years). The prerevision functional score of the patients with knee prosthesis ranged from 36 to 76 (mean, 58) by Hospital for Special Surgery (HSS) Knee Score (Insall et al. 1976).

Another 20 patients with well-functioning stable prosthesis, including 5 subjects with Ti-6Al-4V alloy prosthesis (3 MG-II [Zimmer Co.], 1 MG I), and 1 Microloc (Johnson-Johnson Co., New Brunswick, NJ, USA) and 15 subjects with Co-Cr-Mo alloy prosthesis (8 PCA, 5 Osteonics [Osteonics Co., Allendale, NJ, USA], and 2 Whiteside [Dow Corning Wright Co., Arlington, TN, USA]), were included. All patients underwent non-cemented, porous-coated prosthesis arthroplasty. The mean duration of prostheses implantation was 4.0 years.

The control group consisted of 20 age-matched normal subjects who did not undergo any metal implant surgery. Their ages ranged from 54 to 78 years (mean, 64 years).

We collected the 24 hour urine in the plastic container and sampled 10 ml after well-mixing. The debris was removed by centrifugation. In addition, 10 ml blood was drawn and was heparinized. The contents of metal elements (Ti, Co and Cr) in the blood and urine were performed on a model Z-8200 atomic absorption spectrophotometer (Hitachi, Tokyo) using a graphite furnace (flameless mode). The standard solution was commercially available Ti, Co and Cr standard solution of 1000 ppm (1000 mg/liter) for atomic absorption spectrophotometry. This solution was diluted to 10 ppm by adding 0.1 N nitric acid, and the dilute solution was utilized as a stock solution. The sensitivity of Ti, Co and Cr detection were approximately 5, 1 and 0.4 ppb (μg/liter), respectively. As a sample diluent, 1 g of ammonium phosphate and 1 ml of triton X-100 were diluted with pure water to prepare 100 ml solution. Using this solution, whole blood was diluted to 1/10 and then subjected to measurement. The concentrations were calculated using the standard addition method.

In this study we investigated the metal element concentrations in the blood and urine in the patients with failed non-cemented porous-coated prosthesis arthroplasty. The items to be tested include (1) the metal elements in the whole blood or urine specimen in the patients with loosened or stable prosthesis versus controls; (2) correlation of the metal elements in the blood and urine.

Results

The metal element concentrations in the whole blood were from 10.7 to 129 times higher in patients with loosened prostheses than in those with stable prostheses (Table 1). The concentration of Ti was highest in the whole blood of the patients with loosened Ti-6Al-4V prostheses, as compared to those of subjects with stable prostheses or controls (analysis of variance [ANOVA], $p<0.0001$). The concentration of Co was statistically higher in the patients with loosened Co-Cr-Mo prosthesis than those of the patients with stable prosthesis or controls ($p<0.0001$). Furthermore, the concentration of Cr was also statistically higher in the patients with loosened Co-Cr-Mo prosthesis than those with stable prosthesis or controls ($p<0.0001$).

Although the Ti concentration in the urine seemed higher in the patient with loosened Ti-prosthesis than the other groups, the difference was not significant ($p=0.11$). On the other hands, the Co concentration in the urine was not different among patients with loosened prosthesis, those with stable prosthesis and controls ($p=0.44$). Furthermore, the difference among Cr concentrations in urine of the patients with prosthesis, either stable or loosened, and that of controls was not significant ($p=0.06$) (Table 1).

The correlation of the Ti, Co and Cr element concentrations in the whole blood or urine was shown in Table 2. Only 4 subjects with loosened Ti-6Al-4V

Table 1. *Concentration of Ti, Co, and Cr element in the blood and urine.*

	Whole Blood (ppb)	ANOVA (p-value)	Urine (ppb)	ANOVA (p-value)
Ti				
Loosened pros. ($n=4$)	319.6±280.3	<0.0001	10.1±7.5	0.11
Stable pros. ($n=5$)	17.4±9.8		7.4±2.9	
Controls ($n=20$)	9.3±7.1		5.2±3.7	
Co				
Loosened pros. ($n=16$)	116.1±49.2	<0.0001	0.8±0.6	0.44
Stable pros. ($n=15$)	0.9±0.9		0.9±0.5	
Controls ($n=20$)	0.8±0.5		0.7±0.4	
Cr				
Loosended pros. ($n=16$)	108.1±40.7	<0.0001	1.1±0.7	0.06
Stable pros. ($n=15$)	10.1±2.9		1.1±0.7	
Controls ($n=20$)	5.8±2.6		0.6±0.5	

Data presented as meas ±s.d.

TABLE 2. *Correlation between the blood and urine concentrations.*

	Loosened prostheses	Stable prostheses
Ti	0.918 (n=4)	0.197 (n=5)
Co	0.348* (n=16)	0.092 (n=15)
Cr	0.546* (n=16)	0.020 (n=15)

*$p<0.05$.

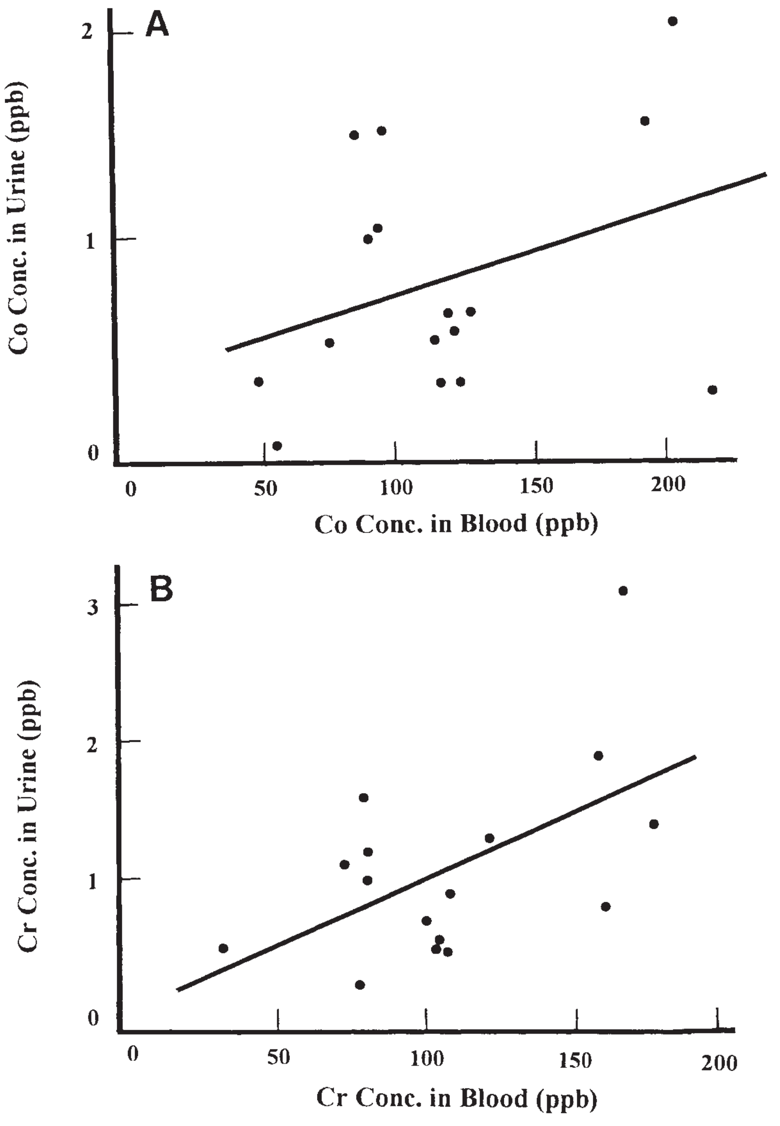

Fig. 1. The linear regression equation of the metal element concentrations in the urine and blood in patients with loosened prosthesis. A: The linear regression equation of Co; CoU=0.326+0.004 CoB (r=0.348, $p<0.05$) (CoU, concentration in the urine; CoB, concentration in blood). B: The linear regression equation of Cr; concentration in urine (CrU) and that in blood (CrB) was CrU=0.058 + 0.095 CrB (r=0.546, $p<0.05$).

alloy prosthesis were available for analysis. No correlation for the Ti concentrations in blood and urine was found in the subjects with loosened or stable prostheses. On the other hand, a moderate positive relationship was demonstrated in the blood and urine concentration for Co ($r=0.348$, $p<0.05$) or Cr ($r=0.546$, $p<0.05$) in the patients with loosened prostheses.

The linear regression equation of the urine concentration (CoU) and blood concentration (CoB) of Co in the patients with loosened prostheses was $CoU=0.326+0.004\ CoB$ (Fig. 1A). The linear regression equation of the urine concentration (CrU) and blood concentration (CrB) of Cr in the patients with loosened prostheses was $CrU=0.058+0.095\ CrB$ (Fig. 1B). However, no correlation for the blood and urine metal element concentrations was found in the subjects with stable prostheses.

Discussion

This study demonstrated that the metal element concentrations in the whole blood, either Ti, Co, or Cr, was statistically higher in the patients with loosened cementless total knee prosthesis than other groups ($p<0.0001$). However, the urine concentrations of metal element did not show any statistical significance in these three groups. A moderate positive relationship between the metal element concentrations, either Co or Cr elements, in whole blood and urine was shown in the patients with loosened prostheses. Hence, high blood concentrations of metal elements may indicate a loosening of cementless prosthesis. The urine concentration was not a good indicator for loosening of prosthesis.

Although there has been shown a wide range of the individual burden of the trace metal elements either in normal subjects or patients with joint implant, concentration of metal elements has been reported to be elevated in the body fluids after the total joint arthroplasty with metal implant, either cemented or cementless arthroplasty (Dobbs and Minski 1980; Black et al. 1983; Pazzaglia et al. 1986; Stulberg et al. 1987; Agins et al. 1988; Lombardi et al. 1989; Sunderman et al. 1989; Dorr et al. 1990; Harris 1991; Lewis et al. 1991; Michel et al. 1991; Brien et al. 1992; Langkamer et al. 1992; Salvati et al. 1993). The present study showed the elevated concentration of metal elements in the blood and urine of patients after the total knee arthroplasty. In addition, the metallosis staining of metal particles produced by wearing was shown in the revision surgery and corresponded to the previous reports (Mirra et al. 1976; Cracchiolo and Revell 1982; Black et al. 1990; Dorr et al. 1990; Witt and Swann 1991; Matsuda et al. 1992; Breen and Stoker 1993; Maloney and Smith 1995). The metallosis may be related to the in vivo corrosion process within the aggressive environment of the human body. The amount of corrosion depends on many factors, including chemical, biological and biomechanical factors, such as the components of alloy, inflammatory reaction of the macrophages, biocompatibility, types of porous coating and the loosening status of the prosthesis, etc. The corrosion products will release the soluble metal elements which may be visible or invisible depending on the components of alloy, e.g., the titanium metallosis is black-looking while the corrosion products of cobalt-chrome alloy is colorless.

After the release of the metal elements, the remote distribution of metal elements would influence their late metabolic effects. The released metal elements may form complexes with serum protein and be excreted through the urine, stool, saliva, sweat, or may be phagocytosed by the foreign body giant cells or macrophages and deposited in the local areas (Rae 1975, 1986; Gruen et al. 1979; Agins et al. 1988; Bullough et al. 1988; Engh and Bobyn 1988; Horowitz et al. 1988, 1993; Lombardi et al. 1989; Bobyn et al. 1990, 1992; Dorr et al. 1990; Harris 1991; Langkamer et al. 1992; Callaghan 1993; Santavirta et al. 1993; Weingart et al. 1994; Maloney and Smith 1995). After phagocytosis by the macrophages, they may be transported by the phagocytes to the lymphoreticular systems. The phagocytosed metal elements also may induce the release of inflammatory mediators or cytokines which can induce further cellular cytotoxicity and trigger an osteolytic response related to the loosening of prosthesis. Therefore the release of the metal particles produced by wearing is one of the most important mechanism causing periprosthetic osteolysis and loosening (Gruen et al. 1979; Tetlebaum and Kahn 1980; Zaidi et al. 1987; Agins et al. 1988; Engh and Bobyn 1988; Horowitz et al. 1988, 1993; Baron 1989; Bobyn et al. 1990, 1992; Santavirta et al. 1990, 1993; Callaghan 1993).

The soluble metal elements in the body mainly form complexes with proteins in the body fluids. There exists a diffusible fraction between the local interstitial fluid and the circulation fluids, i.e., the ability of metal elements to form complexes with the proteins in the body fluids or on the cell membranes is different. Therefore the metabolic fate of the various metal elements differs. Basically, this study revealed a significantly higher concentration of specific metal elements in the blood of patients with arthroplasty, i.e., higher Ti concentration was present in the blood of patients with Ti-prosthesis and higher Co/Cr concentration was present in the patients with Co-Cr-prosthesis. These results were corresponding to the other series (Dorr et al. 1990).

The urine concentration of metal element in the patients with loosening or stable prosthesis was not different from the controls in our series. Although previous investigations showed an increase of urine metal element concentration (Jones and Hungerford 1987; Stulberg et al. 1987; Sunderman et al. 1989; Brien et al. 1992), this would appear in the early postoperative period. In our subjects, the urine samples were collected several years after initial operation. In addition, the urine concentration was dependent on kidney function, including the renal filtration rate, reabsorption function and secretion ability of the kidney. The other possible mechanism of the low urine concentration may be caused by the binding of elements on the red blood cells which are not infiltrated through glomeruli.

The concentrations of metal element in the joint fluid was not studied in this series. In fact, the synovial fluid was not easily available in the clinical practice. The concentration of metal elements in the synovial fluids may be influenced by the amount of the joint fluids. Large amount of the synovial fluids would decrease the concentration of metal elements. Sometimes the patients have not adequate amount of joint fluids for measurement. Some studies showed a higher concentration of metal elements in patients with loosening cemented or cementless prosthesis (Dorr et al. 1990; Brien et al. 1992; Salvati et al. 1993). Furthermore, previous studies also failed to demonstrate a good correlation between histologic finding and the serum levels of metal elements (Dobbs and Minski 1980; Dorr et al. 1990; Lewis et al. 1991). The possible mechanism of this phenomenon may be related to the surgeon's bias, i.e., surgeons always selected the darkest regions for measurement. Therefore, analysis of the metal element concentration in the synovial fluid can not afford useful information for further evaluation.

Finally, the element ratio were studied. The component of Co-Cr alloy (ASTM F-75) is composed of Co (60–64%), Cr (27–30%), Mo (5–7%) and Ni, Mg, Fe ($<1\%$). However, the concentrations of Co and Cr in the whole blood was 116.1 ppb and 108.1 ppb respectively, and in urine 0.8 ppb and 1.1 ppb respectively. The Co/Cr element ratio was 2 for alloy, 1 for blood, and 0.7 for urine. These conditions may be related to the different corrosion activities in the body fluids. Cr has more corrosion activity than Co. In addition, Co has higher protein binding activity and Cr has higher excretion rate. Further studies are indicated for evaluation of the clinical significance. The Co-based alloys are more corrosion-resistant and are the most widely used implant materials in the orthopaedic surgery today. These Co-based alloys has been used since 1960s for directly anchored joint replacements and dental implants.

In conclusion, the loosened prosthesis would release the metal elements into body fluids, especially in the blood. The blood concentrations of metal elements provided an indicator of the loosened prosthesis in the patients after total knee arthroplasty. From this study, we emphasized the better measurement using the blood sample than the urine. However, since there was a moderate positive relationship between the blood and urine concentration of Co or Cr in the patients with loosened prostheses, further investigation is essential for the evaluation of the clinical significance of urine concentration.

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