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Katsuhiko Maezawa · Masahiko Nozawa
Tomohiko Hirose · Keiji Matsuda · Motoo Yasuma
Katsuo Shitoto · Hisashi Kurosawa

Cobalt and chromium concentrations in patients with metal-on-metal and other cementless total hip arthroplasty

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Abstract We measured the cobalt and chromium concentrations in the serum and urine of 32 patients with current designed metal-on-metal total hip arthroplasty and 43 patients with conventional metal on ultrahigh molecular weight polyethylene (UHMWPE) cementless total hip arthroplasty. The results of our study showed that the serum and urine chromium concentrations increased in 37.5% and 90.6%, respectively, of 32 patients with well-fixed metal articulation (the mean values were 0.09 μg/dl and 2.2 μg/l, respectively) and also increased in 28.6% and 85.7%, respectively, of 7 patients who received metal-on-UHMWPE articulation with loosened acetabular component or stem made of Co/Cr alloy (the mean values were 0.06 μg/dl and 1.6 μg/l, respectively). On the other hand, the serum and urine cobalt concentrations were below the detection limit in all patients.

Keywords Cobalt and chromium concentrations · Metal-on-metal total hip arthroplasty · Cementless total hip arthroplasty

Introduction

In conventional total hip arthroplasty using a cobalt-chromium alloy femoral head and an ultrahigh molecular weight polyethylene (UHMWPE) articulation, polyethylene debris may lead to the development of osteolysis and aseptic loosening, thus often resulting in the need for revision surgery. As a result, although the old metal articulating prostheses of McKee-Farrer, Ring, and Müller frequently led to metalosis and thus had fallen into disuse, Weber [1] reintroduced the concept of total hip arthroplasty using metal-on-metal articulations with improved clearance, improved metal hardness, and reproducible surfaces. Alternatively, to prevent the occurrence of polyethylene debris, ceramic-on-ceramic total hip arthroplasty has also been developed. In a number of reports, the presence of released metal ion from total hip arthroplasty both locally [2, 3] and systemically have been documented. Metal release occurs due to wear, corrosions, mechanical stress, and fatigue and may therefore be associated with clinical failure of total hip arthroplasty, cutaneous allergic reactions, or the formation of tumors at the site of the implants. Metal-on-metal articulating total hip arthroplasty may help reduce the polyethylene wear, but concerns remain about the true magnitude of metal wear and the long-term effects of local and systemic exposure to metal ions and particles. The purpose of this study was to determine whether cobalt and chromium concentrations in the serum and urine are high in patients who undergo total hip arthroplasty with current design metal articulation rather than with other types of cementless total hip arthroplasty with a cobalt-chromium alloy femoral head and UHMWPE articulation.

K. Maezawa (✉) · M. Nozawa · T. Hirose · K. Matsuda
M. Yasuma · K. Shitoto · H. Kurosawa
Department of Orthopaedics, Juntendo University School of Medicine, 2–1-1 Hongo, Bunkyo-ku, Tokyo 113–8421, Japan
e-mail: maeza@med.juntendo.ac.jp,
Tel.: +81-3-38133111, Fax: +81-3-38133428

Patients and methods

At Juntendo University Hospital, patients undergoing primary total hip arthroplasty for osteoarthritis, rheumatoid arthritis, and osteonecrosis of the femoral head were implanted with either Lord Mark II type prostheses (in 90 patients from 1987 to 1995), Lord LFR type prostheses (in 60 patients from 1990 to 1992), Omnifit type prostheses (in 50 patients from 1994 to 1997), our original Ti_6Al_4V porus-coated prostheses (in 15 patients from 1997 to 1998), or prostheses with current metal articulation (in 88 patients from 1998 to July 2000). All prostheses were implanted without bone cement. Seventy-five subjects were selected from those patients who received Lord Mark II type prostheses (17 patients), Lord LFR type prostheses (16 patients), our original prostheses (10 patients), and metal-on-metal type prostheses (32 patients). Any patients with other metallic implants, dental prostheses with cobalt and chromium alloys, or those who underwent bilateral total hip arthroplasties or revision arthroplasty were excluded from this study. Four patients who did not have an implant served as control. A total of seven groups was evaluated.

Group 1 comprised 32 patients who had received a metal-on-metal total hip arthroplasty (METASUL; manufactured by

SULZER MEDICA, Switzerland). All had a well functioning prosthesis, and none had radiographic evidence of loosening or osteolysis at follow-up. The mean age of the 8 men and 24 women at the time of blood and urine examinations was 65 years (range 26–79 years). The blood and urine examinations were investigated at 12 months after the operation.

Group 2 comprised 17 patients who had undergone Lord Mark II type cementless total hip arthroplasty (manufactured by Howmedica). Lord Mark II prostheses are constituted from a beaded-coated femoral stem, a modular ball-head, and a metal-backed UHMWPE acetabular component, and all components were made of cobalt-chromium-alloy (ASTM F75). Moreover, group 2 was further divided into two subgroups based on whether they had loosening (group 2-A) or not (group 2-B) according to the radiographical findings. With Lord Mark II prostheses, the femoral stem has maintained a good stability over a long period of time. On the other hand, the acetabular component has a truncated ellipsoid form with no porus coating and a threaded ring design, and was implanted by screwing. The initial stability of the acetabular component was remarkably good, but bone ingrowth did not occur during the postoperative course. As a result, loosening of the acetabular component may occur along with osteoporosis over time [4]. For these reasons, there is a significant difference in the mean duration since the operation between groups 2-A and 2-B. The mean ages closely correlated for groups 2-A and 2-B.

Group 2-A comprised 7 patients. A man and 4 women showed loosened acetabular components, while 1 man and 1 woman had a loosened stem. The mean age of the 7 patients at the time of blood and urine examinations was 71.1 years (range 57–85 years). The mean duration from operation to examination was 127.0 months (range 73–160 months).

Group 2-B comprised 10 patients. The mean age of the 2 men and 8 women at the time of the blood and urine examination was 69.6 years (range 60–80 years). The mean duration from operation to examination was 86.7 months (range 54–156 months).

Group 3 comprised 16 patients who had undergone Lord LFR cementless total hip arthroplasty. The Lord LFR prosthesis was constituted from a flute-shaped femoral stem made of a cobalt-chromium alloy (ASTM F799-82) and a modular ball-head, and a metal-backed (made of Ti_6Al_4V; ASTM F136) UHMWPE acetabular component. Similarly to group 2, group 3 was divided into two subgroups based on whether the patients showed loosening (group 3-A) or not (group 3-B) according to the radiographical findings. In Lord LFR prostheses, loosening of the femoral stem tends to occur within a short time after replacement due to a mechanical weakness for rotational stability [4]. As a result, the patients in groups 3-A and 3-B were matched according to the mean duration since the operation.

Group 3-A comprised 8 patients. Four women showed loosened acetabular components, while four women demonstrated a loosened stem. The mean age of the 8 patients at the time of blood and urine examinations was 73.0 years (range 59–85 years). The mean duration from operation to examination was 94.0 months (range 84–108 months).

Group 3-B comprised 8 women. Their mean age at the time of blood and urine examinations was 64.6 years (range 54–75 years). The mean duration from operation to examination was 90.3 months (range 84–102 months).

Group 4 comprised 10 women who received a Ti_6AL_4V stem with a cobalt-chromium alloy modular ball-head and a metal-backed (made of Ti_6Al_4V; ASTM F136), porus-coated UHMWPE acetabular component without cement. All had well functioning prostheses, and none had any radiographic evidence of loosening or osteolysis at the follow-up intervals of 9 and 12 months (mean 11 months). The mean age of the women at the time of blood and urine examinations was 65.8 years (range 52–78 years).

Group 5 comprised 4 women who did not have an implant and served as a control. Their mean age was 44.3 years (range 20–54 years) (Table 1).

The concentrations of cobalt and chromium in the serum and urine were measured by atomic absorption spectrophotometry. The detection limits were 0.1 ppm for the concentrations of cobalt in the serum and urine, 0.02 μg/dl for chromium in the serum, and 0.2 μg/l for chromium in the urine and were determined by the Mitsubishi Kagaku Biochemistry Laboratories (Tokyo, Japan).

An analysis of the data was performed using the post-hoc Scheffe's test. All values below the detection limits of chromium in the serum and urine were defined as the mean value of 0.01 μg/dl and 0.1 μg/l, respectively, for all statistical caluculations. A value of $p<0.05$ was considered to be statistically significant.

Table 1 Details of the 79 patients analyzed: patients in group 1 underwent well-fixed, current designed, metal-on-metal total hip arthroplasty; those in group 2-A, loosened Lord Mark II type (constituted from beaded-coated femoral stem, modular ball-head, and metal-backed UHMWPE acetabular component, all components were made of Co-Cr alloy); those in group 2-B, well-fixed Lord Mark II type; those in group 3-A, loosened Lord LFR type (constituted from fluted structure femoral stem made of cobalt-chromium alloy (ASTM F799–82) and modular ball-head, and metal-backed (made of Ti_6Al_4V; ASTM F136; UHMWPE acetabular component); those in group 3-B, well-fixed Lord LFR type; those in group 4, our original prostheses [Ti_6AL_4V stem with a cobalt-chromium alloy modular ball-head and metal-backed (made of Ti_6Al_4V; AST M F136) with porus-coated, ultra-high molecular weight polyethylene acetabular component without cement] (well-fixed); those in group 5, no implant as control

Group	No. of patients	Sex distribution Male/female	Loose component Stem/socket	Mean age (years) (range)	Mean duration of implantation (months) (range)
1	32	8/24	0	65.0 (26–79)	12
2-A	7	2/5	2/5	71.1 (57–85)	127.0 (73–170)
2-B	10	2/8	0	69.6 (60–80)	86.7 (54–166)
3-A	8	0/8	4/4	73.0 (59–85)	94.0 (84–108)
3-B	8	0/8	0	64.6 (54–75)	90.3 (84–102)
4	10	0/10	0	65.8 (52–78)	11 (7–12)
5	4	0/4	–	44.3 (20–54)	

Results

The results of our study showed the serum and urine cobalt concentrations to be below the detection limit in all patients. On the other hand, the serum and urine chromium concentrations increased in some patients in groups 1, 2, and 3, but were below the detection limits in all patients in groups 4 and 5. All patients whose serum chromium concentrations were increased also showed increases in their urine chromium concentrations.

In group 1, the mean serum and urine chromium concentrations of the 32 patients were 0.09 μg/dl (range 0.01–0.21 μg/dl) and 2.2 μg/l (range 0.1–5.8 μg/l) (Fig. 1 and 2). The serum chromium concentration increased in 25 (78.1%) and the urine chromium concentration increased in 29 (90.6%) out of 32 patients. The mean serum chromium concentration of the 25 patients was 0.11 μg/dl (range 0.03–0.21 μg/dl), and the mean urine chromium concentration of the 29 patients was 2.4 μg/l (range 0.3–5.8 μg/l). (Tables 2 and 3).

In group 2-A, the mean serum and urine chromium concentrations of the 11 patients were 0.024 μg/dl (range 0.01–0.06 μg/dl) and 1.3 μg/l (range 0.1–3.1 μg/l) (Figs. 1 and 2). The serum chromium concentration increased in 2 (28.6%) out of 7 patients, and both had loosened acetabular components, and the mean serum chromium concentration was 0.06 μg/dl (in both patients). The urine chromium concentration increased in 6 (85.7%) Five had loosened acetabular components, and one had a loosened stem, and the mean urine chromium concentration was 1.6 μg/l (range 0.5–3.1 μg/l). In the remaining patient (14.3%)

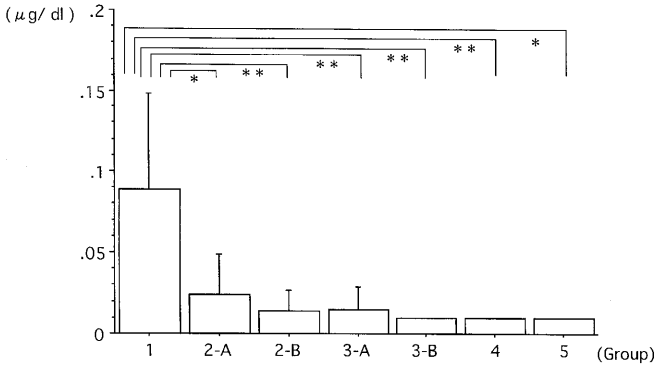

Fig. 1 Mean serum chromium concentrations in each group. All values below the detection limit of chromium in the serum and urine were defined as the mean value of 0.01 μg/dl. Standard deviation denoted by *error bars*. The differences were significant between group 1 and group 2-A (*p<0.05), group 1 and group 2-B (**p<0.01), group 1 and group 3-A (**p<0.01), group 1 and group 3-B (**p<0.01), group 1 and group 4 (**p<0.01), group 1 and group 5 (*p<0.05)

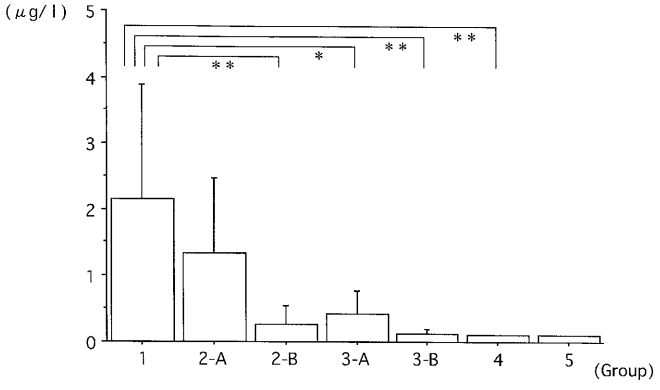

Fig. 2 Mean urine chromium concentrations in each group. All values below the detection limit of chromium in the serum and urine were defined as the mean value of 0.1 μg/l. Standard deviation denoted by *error bars*. The differences were significant between group 1 and group 2-B (**p<0.01), group 1 and group 3-A (*p<0.05), group 1 and group 3-B (**p<0.01), group 1 and group 4 (**p<0.01)

Table 2 Concentrations of chromium in the serum

Group	No. above the detection limit/total samples	Mean concentration (μg/dl)[a] (range)
1	25/32 (78.1%)	0.09 (0.01–0.21)
2-A	2/7[b] (28.6%)	0.06
2-B	1/10[c] (10%)	0.05
3-A	1/8[d] (12.5%)	0.05
3-B	0/8 (0%)	
4	0/10	
5	0/4	

[a]Mean includes only the values that were above the detection limit
[b]Two had loosened acetabular components
[c]Two showed wear of UHMWPE
[d]One had loosened stem

Table 3 Concentrations of chromium in the urine

Group	No. above the detection limit/total samples	Mean concentration (μg/l)[a] (range)
1	29/32 (90.6%)	2.4 (0.3–5.8)
2-A	6/7[b] (85.7%)	1.6 (0.5–3.1)
2-B	4/10[c] (40%)	0.5 (0.3–1.0)
3-A	5/8[d] (62.5%)	0.6 (0.4–1.1)
3-B	1/8 (12.5%)	0.3
4	0/10	
5	0/4	

[a]Mean includes only the values that were above the detection limit
[b]Five had a loosened acetabular component, and one had a loosened stem
[c]Two had wear of UHMWPE
[d]Three had a loosened acetabular component, and two had a loosened stem

who had a loosened stem, the serum and urine concentrations were below the detection limits (Tables 2 and 3).

In group 2-B, the mean serum and urine chromium concentrations of the 7 patients were 0.014 μg/dl (range 0.01–0.05 μg/dl) and 0.26 μg/l (range 0.1–1.1 μg/l) (Figs. 1 and 2). The serum chromium concentration increased in 1 (10%) out of 10 patients, who showed radiographic signs of wear of UHMWPE, the value was 0.05 μg/dl. The urine chromium concentration increased in 4 patients (40%), the mean urine chromium concentration was 0.5 μg/l (range 0.3–1.0 μg/l). In 2 of 4 patients, wear of UHMWPE was radiographically observed. In the remaining 6 patients (60%), the serum and urine concentrations were below the detection limits (Tables 2 and 3).

In group 3-A, the mean serum and urine chromium concentrations of the 32 patients were 0.015 μg/dl (range 0.01–0.05 μg/dl) and 0.43 μg/l (range 0.1–1.1 μg/l) (Figs. 1 and 2). The serum chromium concentration increased in 1 (12.5%) out of 8 patients, the value was 0.05 μg/dl, and this patient showed a loosened stem. The urine chromium concentration increased in 5 (62.5%), the mean concentration was 0.6 μg/l (range 0.4–1.1 μg/l), three had a loosened acetabular component and two had a loosened stem. In the remaining 3 patients (37.5%), 2 had a loosened stem, and 1 had a loosened acetabular component, the serum and urine chromium concentrations were below the detection limits (Tables 2 and 3).

In group 3-B, the mean serum and urine chromium concentrations of the 9 patients were 0.01 μg/dl (range 0.01–0.01 μg/dl) and 0.13 μg/l (range 0.1–0.3 μg/l) (Figs. 1 and 2). The urine chromium concentration increased in 1 (12.5%) out of 8 patients, and the value was 0.3 μg/l. In the remaining 7 patients (87.5%), the serum and urine chromium concentrations were below the detection limits (Tables 2 and 3).

The differences in the mean serum chromium concentrations of each group were significant between group 1 and group 2-A (*$p<0.05$), group 1 and group 2-B (**$p<0.01$), group 1 and group 3-A (**$p<0.01$), group 1 and group 3-B (**$p<0.01$), group 1 and group 4 (**$p<0.01$), group 1 and group 5 (*$p<0.05$) (Fig. 1). The differences in the mean urine chromium concentrations of each group were significant between group 1 and group 2-B (**$p<0.01$), group 1 and group 3-A (*$p<0.05$), group 1 and group 3-B (**$p<0.01$), group 1 and group 4 (**$p<0.01$) (Fig. 2).

Discussion

The articulating surfaces (ball-head) of many modern implants of total hip arthroplasty, excluding ceramic-on-ceramic type prostheses and stems using polymethylmethacrylate, are made from Co/Cr/Mo alloys. Under these conditions, metal release occurs due to wear and tear, modular head-neck corrosion [5, 6], mechanical stress, and fatigue. Wear debris from a total joint replacement has been observed in the periarticular tissue [7, 8] and in distant solid tissue [9, 10]. Case et al. [9] demonstrated high tissue concentrations of metals, including chromium, in the lymph nodes and bone marrow in postmortem studies of patients with worn hip prostheses. Urban et al. [10] reported that metallic wear particles in the liver or spleen were more prevalent in patients who had failed hip arthroplasty than in patients who had had a primary hip or knee replacement.

There is a considerable body of literature concerning the presence of released metal ions which occurs from prosthetic materials, especially from total hip arthroplasty, locally [11] and systemically. Previous articles including blood and urinary studies are classfied into various types in order to compare the different prostheses, materials, and other factors. Concerning metal articulation, Jacobs et al. [12] stated that McKee-Farrar total hip replacements showed a 9-fold elevation in serum chromium, 35-fold elevation in the urine chromium, and 3-fold elevation in the serum cobalt concentrations in comparison with the controls. Brodner et al. [13] stated that modern metal-on-metal articulations produced detectable serum cobalt levels which were significantly different from those of the ceramic-on-polyethylene articulations. Concerning loosened components, Kreibich et al. [14] stated that aseptic loosening of a component resulted in a significant elevation of serum cobalt in the patients who underwent uncemented porous-coated arthroplasty. Jacobs et al. [15] stated that serum concentrations of titanium were elevated approximately 2-fold in those patients who had a loosened component made of titanium-base alloy, compared with the values for the control subjects.

In our study, we observed a significant elevation in the serum and urine chromium concentrations, but not of cobalt, in the patients who had undergone a total hip arthroplasty with modern metal articulation (group 1) and with aseptically loosened components made of Co/Cr alloy (groups 2-A and 3-A). In the patients of group 1 who underwent total hip arthroplasty with modern metal articulation, the elevation rates and concentrations of serum and urine chromium were high as expected. In previous studies of modern metal articulating total hip arthroplasties [12, 13, 16], elevations of the cobalt concentration in the serum and urine were reported, but our study showed them to be below the detection limits in all patients with modern metal articulation. Moreover, the mean concentration of chromium in the serum (0.09 μg/dl) was lower than the values noted in previous reports [12, 16]. The mean values of previous reports, Jacobs et al. [12] and Schaffer et al. [16] reported, were 3.86 ppb (=0.386 μg/dl) and 2.2 μg/l (=0.22 μg/dl). On the other hand, the mean concentration of chromium in the urine (2.2 μg/l) was almost equal to the previous reports, 5.10 ppb (=5.10 μg/l) in Jacobs et al. [12] and 2.7 μg/l in Schaffer et al. [16]. However, the concentrations of each subject concerns the sensitivity of each laboratory [the detection limits of serum and urine chromium in Jacobs's study and ours were 0.03 ppb (=0.003 μg/dl) and 0.02 μg/dl, 0.015 ppb (=0.015 μg/l) and 0.2 μg/l, respectively]. In the patients of group 2-A who received a Co/Cr alloy stem and a Co/Cr alloy socket without cement, and in whom later the stem or acetabular component became loosened, serum and

urine chromium increased in 28.6% (mean serum concentration 0.06 μg/dl) and 85.7% (mean urine concentration 1.6 μg/l) of the patients, respectively. Most of the patients whose serum and urine concentrations increased had loosened acetabular components, and thus these findings are considered be associated with aseptic loosening of the acetabular components. In the patients of group 3-A who received a Co/Cr alloy stem and a titanium alloy socket without cement, when either a stem or an acetabular component had become loosened, the serum and urine chromium levels increased in 12.5% (mean serum concentration 0.05 μg/dl) and 62.5% (mean urine concentration 0.6 μg/l) of the patients, respectively. Owing to the fact that the acetabular component was made of a titanium alloy in group 3-A, these findings were thought to be associated with either an aseptic loosening of the stem or head-neck corrosion.

In metal-on-metal articulating total hip arthroplasty, concerns remain about the true magnitude of metal wear and the long-term effects of local and systemic exposure to metal ions and particles. Some epidemiological studies of cancer risk after total hip replacement have been reported. Gillespie et al. [17] and Mathiessen et al. [18] observed a significant increase in leukemia and lymphomas during the first postoperative year. Visuri et al. [19] reported that the leukemia rate of the patients who had metal-on-metal total hip arthroplasty (1960s prostheses) was 3.77-fold compared with that of the patients who underwent polyethylene on metal total hip arthroplasty. However, these articles investigated patients who received a McKee-Farrer prosthesis, and the incidence of cancer risk does not necessarily correspond to modern metal-on-metal prostheses. On the other hand, they reported that other cancer risks were low in patients with metal-on-metal total hip arthroplasty compared with the controls. Nylene et al. [20] stated that in their largest study to date evaluating hip replacement and subsequent cancer risk, the overall cancer risk appears to be negligible from a public health perspective, and thus no strong evidence exists against the continued use of hip replacement.

Cobalt and chronium are known to be essential trace metals; their depletion in the body consistently results in a physiological deficiency syndrome, and specific repletion reverses these abnormalities. Cobalt, a co-factor in vitamin B12, and chromium, an essential co-factor in the interaction between insulin and its receptor, are toxic in sufficiently high quantities in vivo [21]. Increased levels of cobalt can induce polycythemia and testicular toxicity and can also interfere with DNA repair. Hexavalent chromium, a possible implant-degradation product, has been characterized as a class-I human carcinogen. Despite the longstanding recognition of the toxicity of some of these elements both in in vitro and in animal models, the relationship between cancer risk and the amount of released metal debris into body fluids has yet to be elucidated. World-wide long-term studies are thus needed to determine the risk of metal-on-metal total hip arthroplasty and other implants as a potential cause of cobalt and chromium toxicity.

References

1. Weber BG (1992) Metal-metal pairing in total-hip-replacement: back to the future. Z Orthop 130: 306
2. Betts F, Wright T, Salvati EA, Boskey A, Bansal M (1992) Cobalt-alloy metal debris in periarticular tissues from total hip revision arthroplasties. Clin Orthop 276: 75
3. Huo MH, Salvati EA, Lieberman JR, Betts F, Bansal M (1992) Metallic debris in femoral endosteolysis in failed cemented total hip arthroplasties. Clin Orthop 276: 157
4. Shitoto K (1994) Roentgenological follow-up of Lord-type cementless total hip arthroplasty. (in Japanese) J Jpn Orthop Assoc 68: 390
5. Jacobs JJ, et al (1998) Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am 80: 1447
6. Jacobs JJ, Urban RM, Gilbert JL,Skipor AK, Black J, Jasty M, Galente JO (1995) Local and distant products from modularity. Clin Orthop 319: 94
7. Dorr LD, Bloebaum R, Emmanual J, Meldrum R (1990) Histologic, biochemical, and ion analysis of tissue and fluids retrieved during hip arthroplasty. Clin Orthop 261: 82
8. Lee JM,Salvati EA, Betts F, DiCarlo E, Doty SB, Bullough P (1992) Size of metallic and polyethylene debris particles in failed cemented total hip replacement. J Bone Joint Surg Br 74: 380
9. Case CP, Langkamer VG, James C, Palmer MR, Kemp AJ, Heap PE, Solomon L (1994) Widespread dissemination of metal debris from implants. J Bone Joint Surg Br 76: 701
10. Urban RM, Jacob JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M (2000) Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. J Bone Joint Surg Am 82: 457
11. Brien WW, Salvati EA, Betts F, Bullough P, Wright T, Rimnac C, Buly R, Garvin K (1992) Metal levels in cemented total hip arthroplasty. A comparison of well-fixed and loose implants. Clin Orthop 276: 66
12. Jacobs JJ, Skipor AK, Doorn PF, Campbell P, Schmalzried TP, Black J, Amstutz HC (1996) Cobalt and chromium concentrations in patients with metal on metal total hip replacements. Clin Orthop 329S: S256
13. Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R (1997) Elavated serum cobalt with metal-on-metal articulating surfaces. J Bone Joint Surg Br 79: 316
14. Kreibich DN, Moran CG, Delves HT, Owem TD, Pinder IM (1996) Systemic release of cobalt and chromium after total hip replacement. J Bone Joint Surg Br 78: 18
15. Jacobs JJ, Skipor AK, Black J, Urban RM, Galente JO (1991) Release and excretion of metal in patients who have a total hip-replacement component made of titanium-base alloy. J Bone Joint Surg Am 73: 1475
16. Schaffer AW, Pilger A, Engelhardt C, Zweymueller K, Ruediger HW (1999) Increased blood cobalt and chromium after total hip replacement. Clin Toxicol 37: 839
17. Gillespie WJ, Frampton CMA, Henderson RJ, Ryan PM (1988) The incidence of cancer following total hip replacement. J Bone Joint Surg Br 70: 539
18. Mathiessen EB, Ahlbom A, Bermann G, Lindgren JU (1995) Total hip replacement and cancer. J Bone Joint Surg Br 77: 345
19. Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska EB (1996) Cancer risk after metal on metal and polyethylene on metal total hip arhtroplasty. Clin Orthop 329S: S280
20. Nylene O, McLaughlin JK, Gridley G, Ekbom A, Johnell O, Fraumeni JF Jr, Adami H (1995) Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. J Natl Cancer Inst 87: 28
21. Angle CR (1995) Organ-specific therapeutic intervention. In: Geoyer RA, Klaasen CD, Waalkes MP (eds) Metal toxicology. Academic Press, San Diego