Adverse Tissue Reactions and Metal Ion Behavior After Small-Head Metasul Hip Arthroplasty: A Long-Term Follow-Up Study

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Objective: To investigate the long-term survivorship, incidence of adverse reactions to metal debris (ARMD), and metal ion behavior in patients who underwent small-head Metasul metal-on-metal (MoM) total hip arthroplasty (THA).

Methods: Between February 1998 and September 2003, a retrospective study was performed on 43 consecutive patients (43 hips) who underwent unilateral cementless Metasul MoM THAs at our institution. Of them, 35 patients (nine males and 26 females) who were available for follow-up more than 15 years after THA were enrolled in this study and underwent metal artifact reduction sequence magnetic resonance imaging (MARS-MRI) to identify ARMD. The mean age at surgery of the patients was 59.7 years old (range, 31–83). Clinical and radiographic outcomes were evaluated retrospectively. Clinical examinations were conducted using the Harris Hip Score (HHS). Serum cobalt (Co) and chromium (Cr) ion levels and Co/Cr ratio were assessed at different postoperative periods of <5, 5–10, 11–14, and ≥15 years.

Results: The mean follow-up period for the 35 patients included was 18.1 years (range, 15–22). The mean HHS significantly improved from 44.6 ± 11.3 points preoperatively to 89.4 ± 7.9 points at the final follow-up (P < 0.0001). ARMD was found in 20% of the patients using MARS-MRI. No signs of stem loosening were found clinically or radiographically, whereas cup loosening and ARMD were observed in three patients (9%), for whom revision THAs were performed. The Kaplan–Meier survival rates with revision for any reason as the endpoint were 90.9% at 5 years, 84.8% at 10 years, 84.8% at 15 years (95% CI, 67.1–93.6), and 70.3% at 20 years (95% CI, 43.6–87.0). The survival rates with revision for ARMD as the endpoint were 100% at 5 years, 96.6% at 10 years, 96.6% at 15 years (95% CI, 77.2–99.7), and 80.1% at 20 years (95% CI, 45.3–95.2). Serum Co ion level peaked at 5–10 years after THA, which was significantly higher than that <5 years; however, it decreased to the initial level after 15 years. In contrast, serum Cr ion level significantly increased at 5–10 years and then remained almost constant. Significant differences in Cr ion levels (1.0 vs 2.0 μg/L, P = 0.024) and Co/Cr ratio (1.3 vs 0.9, P = 0.037) were found between non-ARMD and ARMD patients at >11 years postoperatively.

Conclusion: Our results suggest that increased Cr ion levels and decreased Co/Cr ratio may be signs of ARMD in patients who underwent small-head Metasul MoM THA.

Key words: Adverse reactions to metal debris; Metal ion levels; Metal-on-metal; Metasul; Small head

Introduction

Metal-on-metal (MoM) bearing was clinically introduced in the 1960s to prevent periprosthetic osteolysis and aseptic loosening associated with implant articulation wear in total hip arthroplasty (THA). However, the first-generation MoM THA exhibited unsatisfactory outcomes due to a high
rate of failure associated with frictional torque complications resulting in locking and seizing with subsequent corrosion of the bearing surfaces. The second-generation MoM bearings such as Metasul (Sulzer Medica, currently Zimmer-Biomet, Warsaw, IN, USA) were developed in the late 1980s using updated technologies including improved bearing tolerances and surface finish, contact-area location, and elimination of bearing recesses. Metasul bearing couple comprised a 28-mm wrought-forged high-carbon (0.2%-0.25%) cobalt-chromium (CoCr) head, and the acetabular liner housed in a non-crosslinked polyethylene insert, which was held in a titanium alloy metal shell. Metasul MoM bearings have shown promising outcomes both in vivo and in vitro. According to the past retrieval study, high-carbon Metasul bearings showed approximately 60 times less wear than metal-on-conventional polyethylene bearings in THA 7. Several clinical studies have reported implant survival rates of over 90% with a minimum of 10 years of follow-up 8.

Despite the excellent wear resistance of metal bearings, some of the latest generation MoM THA have exhibited unexpected high failure rates due to soft tissue inflammatory and immunological reactions to metal debris and ions (adverse reactions to metal debris [ARMD]). The complications include necrosis, lymphocytosis, vasculitis, and the development of pseudotumors. ARMD is commonly associated with mechanically assisted metal corrosion at the head–neck taper interface as well as articulation wear 9–14. Several studies have identified the use of large heads (≥36 mm) as a significant risk factor for ARMD in MoM THA because of large frictional torque at the modular head–neck interfaces 15–17. ARMD is often asymptomatic, and its careful screening is hardly performed before clear symptoms appear. Metal artifact reduced sequence magnetic resonance imaging (MARS-MRI) is the gold standard in diagnosing ARMD, which has some disadvantages including the increased scan time, the obscuration of periprosthetic tissues by metal artifacts, and the cost 9. The levels of blood metal ions have also been monitored for evaluating the risk of ARMD. Cobalt (Co) and chromium (Cr) ion levels and their ratios are considered important biomarkers for diagnosing ARMD 19–21. It has been generally understood in large diameter MoM THA that the higher the serum Co ion level and Co/Cr ratio, the higher the risk of ARMD 22. Bosker et al. 23 reported that patients with elevated serum Co and Cr ion levels had a four-times greater risk of developing a pseudotumor following large-head MoM THA. Haddad et al. 24 reported that 75%–90% of patients with metal ion levels of either Co or Cr above 4 μg/L have ARMD-related complications. A metal ion level greater than 4.5–7.0 ppb (Cr or Co) is currently considered as a potential threshold for the occurrence of abnormal wear, and also as a trigger for a MARS MRI scan or revision surgery 25,26. On the other hand, one clinical study performed by Griffin et al. 27 showed no significant correlation between levels of metal ions and severity of ARMD at the time of the revision, whereas a positive correlation was found between implantation time and the severity of ARMD. The findings suggest that ARMD may be more dependent on an in vivo time of metal exposure rather than on its amount. In this context, they questioned the effectiveness and reliability of the ion level threshold (7 ppb) as a predictor for soft tissue damage based on their results of low sensitivity (Co 61%, Cr 31%) and specificity (Co 58%, Cr 76%) in detecting ARMD. One potential limitation of metal ion measurement is that individual patients have an undefined variable biologic response to metal ions and particles 26, 27. Another limitation can be considered as a time-dependent change in the balance between ion release from the device and ion excretion or storage (or potential consumption for tissue reactions) 28, 29. Therefore, it is of great importance to continuously monitor the long-term metal ion behavior following MoM THA.

Furthermore, in contrast to many reports on large head MoM, the long-term behaviors of in vivo metal ions after small-head MoM (≤28 mm) have been much less studied. Considering less frictional torques generated at head–neck junction and articulation, patients receiving small-head MoM THA may entail a smaller risk of ARMD than those receiving large-head MoM 15–17. Some studies have shown excellent survivorship in small-head MoM bearings 8, 20. An Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) database-based study showed a significantly lower revision rate after small-head MoM THA than after large-head MoM THA. In addition, the cumulative percentages of revision surgeries for ARMD at 15 years were 0.8% (95% CI, 0.8–1.4) for small heads and 12.4% (95% CI, 11.4–13.7) for large heads 30, 31. However, other recent studies have highlighted the late onset of ARMD in small-head MoM THAs, resulting in reduced long-term survivorship 30–32.

In consideration of the above background, we performed the long-term follow-up study on small-head Metasul MoM THA, which was specifically designed in order to clarify the following: (i) the implant survivorship; (ii) incidence of ARMD; and (iii) serum metal ion levels over time. Based on the results, we also attempted to consider the diagnostic potential of metal ion measurement in identifying ARMD.

Materials and Methods

Inclusion and Exclusion Criteria

The inclusion criteria were defined as follows: (i) patients treated with unilateral primary cementless THA; (ii) patients with small-head (28 mm) MoM Metasul bearings; and (iii) patients with complete clinical, radiographic evaluation and MARS-MRI screening for ARMD.

The exclusion criteria were as follows: (i) patients with a history of metal hypersensitivity; and (ii) patients with renal dysfunction potentially affecting serum metal ion levels.

Patients

The institutional review board of our hospital approved this study. We retrospectively collected the medical records included 43 patients who underwent unilateral cementless MoM THAs using small-head (28 mm) Metasul bearings at our institution between February 1998 and September 2003. Among these patients, four died due to reasons unrelated to THA, and four had missing follow-up data for more than
10 years postoperatively. The remaining 35 patients were included in this study and were followed up at a minimum period of 15 years.

**Surgery**

All surgeries were performed on by three senior surgeons (KY, TS, TM) under general anesthesia in the lateral position with a posterior approach. Primary cementless THA was performed with a Metasul MoM bearing in all patients. A cementless straight-tapered stem with a Natural Hip femoral stem (Zimmer-Biomet) was used as the femoral component combined with a 28 mm modular CoCr head in all patients. The femoral component is a proximally porous-coated titanium alloy implant, and its neck was designed with a 12/14 taper. The target acetabular position during surgery was 40° of inclination and 20° of anteversion angle.

**Outcome Measures**

**Clinical and Radiographic Evaluation**

Clinical and radiographic outcomes at a mean follow-up period of 18.1 years (range: 15–22) were evaluated retrospectively. Clinical examinations were conducted using the Harris Hip Score (HHS) (range, 0–100), which was evaluated as poor (<70), fair (70 to 79), good (80 to 89), and excellent (90 to 100). Standard anteroposterior pelvic and lateral radiographs of the hip were obtained at the follow-up visits to evaluate periprosthetic osteolysis and loosening of the component in the seven femoral zones of stem defined by Gruen et al. and three acetabular zones defined by DeLee and Charnley. Cup inclination and anteversion angles were measured using the Martell Hip Analysis Suite software, version 8.0.4.5 (University of Chicago, IL, USA).

**Metal Ion Measurement**

The patients’ serum Co and Cr ion levels were measured using inductively coupled plasma mass spectrometry at Mayo Medical Laboratories (Rochester, MN, USA) and atomic absorption spectrometry at LSI Medience Corporation (Tokyo, Japan). The serum Co and Cr ion levels were examined at different postoperative periods of <5 (median: 1.9, n = 21), 5–10 (median: 7.5, n = 26), 11–14 (median: 12.3, n = 28), and ≥15 (median: 16.5, n = 19) years. Note that we considered <5, 5–10, and >11 years as the early-, mid-, and long-term follow-up periods, respectively. The metal ion levels after revision surgery were excluded from this analysis. The detection limit of both Co and Cr ions was 0.1 μg/L. Additionally, the Co/Cr ratio was analyzed for each patient.

**MARS-MRI Evaluation**

Cross-sectional imaging using metal artifact reduction sequence magnetic resonance imaging (MARS-MRI) using a 1.5-T scanner (MAGNETOM Avanto; Siemens Healthineers, Erlangen, Germany) was performed at a mean postoperative period of 12 years (± standard deviation: 1.5) to diagnose ARMD for all patients (including asymptomatic screening). According to the MRI classification described by Hauptfleisch et al., ARMD was defined as any cystic or solid mass (pseudotumor) with the definite presence of a cyst wall in continuity with the hip joint, excluding isolated distension or thickening of a non-communicating trochanteric bursa. This classification system was based on the compositions and wall thicknesses of the reactive masses on MARS-MRI, dividing them into the following three groups: type I, thin-walled (<3 mm) cystic masses; type II, thick-walled (>3 mm) cystic masses; and type III, predominantly solid masses.

| TABLE 1 Patients’ demographics |
|--------------------------------|
| Demographic                  | Value |
| Number of patients           | 35    |
| Gender (male: female)        | 9: 26 |
| Diagnosis (OA: RA: ION)      | 26: 5: 4 |
| Age at surgery* (year)       | 59.7 (±9.0) |
| Follow-up time* (year)       | 18.1 (±2.4) |
| Body mass index* (kg/m²)     | 23.8 (±3.3) |
| Cup inclination* (°)         | 42.9 (±9.0) |
| Cup anteversion* (°)         | 15.8 (±12.1) |

*Values are presented as the mean (± SD).; ION, idiopathic osteonecrosis of the femoral head; OA, osteoarthritis; RA, rheumatoid arthritis.

| TABLE 2 Detailed information on revised hips |
|---------------------------------------------|
| Case | Age/ Gender | Diagnosis | Reason for revision | Time to revision (years) | Revision procedure                      |
|------|-------------|-----------|---------------------|-------------------------|-----------------------------------------|
| 1    | 55/Male     | ION       | Infection           | 5                       | Two-stage revision of cup and stem      |
| 2    | 58/Male     | ION       | Infection           | 5                       | Two-stage revision of cup and stem      |
| 3    | 69/Female   | OA        | Recurrent dislocation | 5                       | Revision with cup and head exchange     |
| 4    | 64/Female   | OA        | Infection           | 6                       | Two-stage revision of cup and stem      |
| 5    | 62/Female   | OA        | Symptomatic ARMD with cup loosening | 7                       | Revision with cup exchange               |
| 6    | 61/Female   | OA        | Symptomatic ARMD with cup loosening | 16                      | Revision with cup and bone graft        |
| 7    | 50/Female   | RA        | Symptomatic ARMD with cup loosening | 19                      | Revision with cup and bone graft        |

ARMD, adverse reactions to metal debris; ION, idiopathic osteonecrosis of the femoral head; OA, osteoarthritis; RA, Rheumatoid arthritis.
All statistical analyses were performed using the GraphPad Prism software, version 8.4.1 (GraphPad Software Inc., San Diego, CA, USA). The Kaplan–Meier survivorship analysis with 95% confidence intervals (95% CI) was conducted on revision surgeries for any reason and ARMD as the end-points. The Wilcoxon signed-rank and Fisher’s exact tests were conducted to assess the statistical differences in gender percentage between non-ARMD and ARMD patients. The Mann–Whitney U test was conducted to compare the

**Statistical Analysis**

All statistical analyses were performed using the GraphPad Prism software, version 8.4.1 (GraphPad Software Inc., San Diego, CA, USA). The Kaplan–Meier survivorship analysis with 95% confidence intervals (95% CI) was conducted on revision surgeries for any reason and ARMD as the end-points. The Wilcoxon signed-rank and Fisher’s exact tests were conducted to assess the statistical differences in gender percentage between non-ARMD and ARMD patients. The Mann–Whitney U test was conducted to compare the

**Fig. 2** Box plots showing changes in serum cobalt (Co) ion (A), chromium (Cr) ion (B), and Co/Cr ratio (C) over the postoperative period. Co ion level peaked at 5–10 years after surgery and then decreased continuously until the final follow-up. Cr ion levels increased at 5–10 years and remained almost constant until the final follow-up. Co/Cr ratio was the highest at <5 years and then decreased continuously.
TABLE 3 The median values and interquartile ranges of serum cobalt (Co), chromium (Cr) ion levels and Co/Cr ratios at <5, 5–10, 11–14, and ≥15 years postoperatively

| Variable     | Follow-up (years) | Median (IQR) | Kruskal-Wallis test P-value | Dunn’s post hoc test P-value |
|--------------|-------------------|--------------|-------------------------------|-----------------------------|
| Co ion level (µg/L) | <5                | 0.6 (0.5–0.8) | 0.0002*                     |                              |
|              | 5–10              | 1.1 (1.0–3.6) |                               |                              |
|              | 11–14             | 1.0 (0.7–1.8) |                               |                              |
|              | ≥15               | 0.8 (0.8–1.4) |                               |                              |
| Cr ion level (µg/L) | <5                | 0.2 (0.1–0.2) | <0.0001*                     |                              |
|              | 5–10              | 1.0 (0.1–2.0) |                               |                              |
|              | 11–14             | 1.1 (0.6–2.0) |                               |                              |
|              | ≥15               | 1.1 (0.9–2.1) |                               |                              |
| Co/Cr ratio  | <5                | 5.0 (4.8–7.3) | <0.0001*                     |                              |
|              | 5–10              | 2.0 (1.3–10.0) |                               |                              |
|              | 11–14             | 1.1 (0.8–1.4) |                               |                              |
|              | ≥15               | 0.8 (0.6–0.9) |                               |                              |

Their P-values were also provided among the different follow-up periods according to the Kruskal–Wallis test with Dunn’s post hoc comparisons.; IQR, interquartile range.; *P < 0.05.

demographic data between non-ARMD and ARMD patients. The Kruskal–Wallis test was conducted to compare serum Co and Cr ion levels and Co/Cr ratios among the different postoperative periods, and Dunn's multiple comparisons test was used for their pairwise post hoc comparisons. Probability (P) values of <0.05 denote statistical significance.

Results

General Results

The mean follow-up period for the 35 included patients (nine males and 26 females) was 18.1 ± 2.4 years (range, 15–22). The mean age at surgery of the patients was 59.7 years old (range, 31–83). The mean HHS significantly improved from 44.6 ± 11.3 points preoperatively to 89.4 ± 7.9 points at the final follow-up (P < 0.0001). The patients’ demographics and clinical characteristics are summarized in Table 1.

Radiographic Outcomes

The osteolytic lesions of the stem and cup were observed in five patients (14%) and four patients (11%), respectively. All femoral osteolysis were located at the Gruen zone 1 or 7, whereas the acetabular osteolysis were at DeLee and Charnley zone 2 (two patients) and zone 3 (two patients). No signs of stem loosening were found clinically or radiographically, whereas cup loosening was observed in three patients (9%), for whom revision THAs were performed (Table 2). The mean cup inclination and anteversion angles were 42.9° ± 9.0° and 15.8° ± 12.1°, respectively (Table 1).

Complications

In total, seven patients underwent revision surgery for recurrent dislocation (one patient), infection (three patients), and ARMD (three patients) at the postoperative years of 5, 5–6, and 7–19, respectively. The detailed information of all complications in the revised cases are summarized in Table 2.

Implant Survivorship Evaluation

The Kaplan–Meier survival rates with revision for any reason as the endpoint were 90.9% at 5 years, 84.8% at 10 years, 84.8% at 15 years (95% CI, 67.1–93.6), and 70.3% at 20 years (95% CI, 43.6–87.0) (Fig. 1A). The survival rates with revision for ARMD as the endpoint were 100% at 5 years, 96.6% at 10 years, 96.6% at 15 years (95% CI, 77.2–99.7), and 80.1% at 20 years (95% CI, 45.3–95.2) (Fig. 1B).

Metal Ion Levels

Figure 2 shows the serum Co and Cr ion levels and their ratio in all patients examined at different follow-up periods after THA. The median Co and Cr ion levels were lowest at the initial follow-up period of <5 years and increased at 5–10 years (Fig. 2A,B). The median and interquartile range (IQR) of serum Co ion levels (µg/L) were 0.6 (IQR, 0.5–0.8), 1.1 (IQR, 1.0–3.6), 1.0 (IQR, 0.7–1.8), and 0.8 (IQR, 0.8–1.4) at <5, 5–10, 11–14, and ≥15 years, respectively (Table 3). Alternatively, the median serum Cr ion levels (µg/L) were 0.2 (IQR, 0.1–0.2), 1.0 (IQR, 0.1–2.0), 1.1 (IQR, 0.6–2.0), 1.1 (IQR, 0.9–2.1) at <5, 5–10, 11–14, and ≥15 years, respectively. The Kruskal–Wallis test revealed significant differences in serum Co and Cr ion levels among the different follow-up periods (P = 0.0002 and P < 0.0001, respectively). Post hoc analysis using Dunn’s multiple comparison tests showed that serum Co ion levels detected at 5–10 years (P < 0.0001) and 11–14 years (P = 0.0381) were 83% and 67% higher significantly than the Co ion levels at <5 years, whereas serum Cr ion levels detected at 5–10 years (P = 0.0028), 11–14 years (P < 0.0001), and ≥15 years (P = 0.0157) were 400%, 450%, and 450% higher significantly than those detected at <5 years. However, the median
Co/Cr ratio was the highest at <5 years and then decreased continuously (Fig. 2C, Table 3). Significant differences in the serum ion levels over time were more sensitively detected using the Co/Cr ratio instead of each ion level, and post hoc analysis showed the significant differences in the Co/Cr ratio between <5 and 11–14 years (78% decrease, $P < 0.0001$), between <5 and ≥15 years (84% decrease, $P = 0.0019$), between 5–10 and 11–14 years (45% decrease, $P = 0.0116$), and between 5–10 and ≥15 years (60% decrease, $P = 0.0313$).

Comparisons Between Non-ARMD and ARMD Patients
MARS-MRI identified pseudotumor formation in seven patients (20%), suggesting the incidence of ARMD. The pseudotumor was classified as type I (four patients, 57%), type II (one patient, 14%), and type III (two patients, 29%) (Fig. 3A–C). Three of the seven patients underwent revision surgery for symptomatic ARMD and component loosening (Table 2). No obvious signs of fretting corrosion were intraoperatively found at their head–neck junctions in the three

**Fig. 3** Representative postoperative metal artifact reduction sequence magnetic resonance imaging (MARS-MRI) findings of pseudotumor (arrows) classified as Hauptfleisch’s types I (A), II (B), and III (C), respectively. The (A) indicates the coronal MARS-MRI of a 63-year-old female with type I pseudotumor located in front of the left acetabular cup. She was asymptomatic and had an excellent Harris Hip Score (HHS) of 90 points at the final follow-up of 18 years. The (B) indicates the coronal MARS-MRI of a 61-year-old female with a type II pseudotumor located around the femoral neck of the right stem. She underwent revision surgery due to a symptomatic adverse reaction to metal debris (ARMD) with cup loosening at 16 years postoperatively (Case 6 in Table 2). The (C) indicates the coronal MARS-MRI of a 50-year-old female with type III pseudotumor located in the right pelvic cavity. She underwent revision surgery due to symptomatic ARMD with cup loosening at 19 years postoperatively (Case 7 in Table 2).

**Fig. 4** The representative photographs showing no obvious fretting corrosion at taper bore interface of the retrieved metal head (A) and stem trunnion (B) in a patient with adverse reaction to metal debris (ARMD) (Case 6 in Table 2).
TABLE 4 Characteristics of patients with and without adverse reaction to metal debris (ARMD)

| Variable                      | Non-ARMD (n = 28) | ARMD (n = 7) | P value |
|-------------------------------|-------------------|--------------|---------|
| Age at surgery*               | 58.9 (± 9.0)      | 60.3 (±6.7)  | 0.692   |
| Female gender (%)             | 65                | 100          | 0.069   |
| BMI (kg/m²)                   | 23.4 (± 3.3)      | 23.6 (±2.8)  | 0.853   |
| eGFR* (mL/min/1.73 m²)        | 76.9 (±25.2)      | 76.3 (±26.9) | 0.942   |
| HHS* (points)                | 90 (± 6.6)        | 87 (±8.8)    | 0.482   |
| Cup inclination* (°)          | 42 (± 5.8)        | 47 (±8.5)    | 0.296   |
| Cup anteversion* (°)          | 15 (± 11.8)       | 18 (±12.2)   | 0.587   |
| Co ion level† at the mid-term (µg/L) | 1.0 (0.7–1.2) | 1.0 (1.0–11.3) | 0.179   |
| Co ion level† at the long-term (µg/L) | 1.0 (0.1–1.0) | 1.8 (1–2.3)   | 0.158   |
| Cr ion level† at the mid-term (µg/L) | 0.9 (0.8–1.6) | 1.0 (0.3–6.5) | 0.233   |
| Cr ion level† at the long-term (µg/L) | 1.0 (0.3–1.8) | 2.0 (1.1–2.6)  | 0.0241  |
| Co/Cr ratio† at the mid-term  | 1.6 (1.0–5.0)     | 2.1 (1.1–4.4) | 0.654   |
| Co/Cr ratio† at the long-term | 1.3 (1.0–2.9)     | 0.9 (0.7–4.2) | 0.0371  |

Co, cobalt; Cr, chromium; BMI, Body mass index; HHS, Harris hip score; eGFR, Estimated glomerular filtration rate; *Values are presented as the mean (±SD); †Values are presented as the median [IQR]; ° P < 0.05.

ARMD patients (Fig. 4). The remaining four patients had asymptomatic ARMD and had no hip pain, for whom, therefore, revision THA was not performed. The clinical characteristics of non-ARMD and ARMD patients are shown in Table 4. Since all cases of ARMD were found beyond the mid-term follow-ups, the serum ion levels were compared between the groups by the relevant periods (Table 4, Fig. 5). The median serum Co and Cr ion levels and their ratio at the mid-term follow-up (5–10 years) did not differ significantly between non-ARMD and ARMD groups (P = 0.179, P = 0.233, and P = 0.654, respectively). Serum Co ion levels at the long-term follow-up did not significantly differ between the two groups (P = 0.158). However, significant differences were found in the serum Cr ion levels and Co/Cr ratio at the long-term follow-up (P = 0.024 and P = 0.037, respectively). Consequently, the serum Cr ion level was 100% higher (1.0 µg/L [IQR, 0.3–1.8] vs 2.0 µg/L [IQR, 1.1–2.6]), and the Co/Cr ratio was 31% lower (1.3 [IQR, 1.0–2.9] vs 0.9 [IQR, 0.7–1.2]) in the ARMD group than those in the non-ARMD group.

Discussion

The Long-Term Survivorship and Incidence of ARMD

The excellent mid- and long-term outcomes of MoM THA using 28 mm Metasul bearings have been reported. The survival rates were 90%–96% with revision surgery as the endpoint.3–8. Besides, the revision rates associated with ARMD have been reported as 0%–3% only within 15 years following small-head MoM THA.6,8,17,36. A recent study of AOANJRR data showed a significantly lower revision rate after small-head MoM THA than after large-head (>32 mm) MoM THA.37. The revision rates were 27.4% and 8.5% at a 14-year follow-up period of large-head MoM THA and a 15-year follow-up period of small-head MoM THA with a hazard ratio of 5.18 (95% CI, 4.1–6.5; P < 0.001); additionally, the cumulative percentages of revision surgeries for ARMD at 15 years were 0.8% (95% CI, 0.8–1.4) for small heads and 12.4% (95% CI, 11.4–13.7) for large heads. Nevertheless, even using small-head MoM bearings, other recent studies have cautioned elevated metal ion levels and the late onset of ARMD after a long-term in vivo service.30–32. Lombardi et al.31 reported the outcomes of small-head MoM THA using the M2a Taper system (Zimmer-Biomet), whose survival rates at 10, 15, and 19 years were 96%, 92%, and 73%, respectively. Revision THAs were performed in 14/20 hips (70%) due to ARMD. Reiner et al.32 reported that ARMD was found in 41% of the patients implanted with Metasul followed up at a mean period of 15.5 years. In this study, ARMD was found in 20% of the patients implanted with Metasul. Accordingly, the revision rate increased rapidly from 4% to 20% between 15 and 20 years after THA, and the survival rate decreased from 84.8% to 70.3% (Fig. 1). Our results suggest that ARMD is a major postoperative complication beyond 15 years even after small-head MoM THA.

The Long-Term Behavior of Metal Ions and Diagnostic Potential of ARMD

Most investigations on the association between serum metal ion levels and ARMD have involved large-head MoM THA.10,11,23. Bosker et al.23 reported that patients with elevated serum metal ion levels had a four-times greater risk of developing a pseudotumor following large-head MoM THA. Conversely, the long-term behavior of serum metal ion levels after small-head MoM THA is not fully understood. Waldstein et al.37 showed that the median serum Co ion level remained low (1.04 µg/L [IQR, 0.64–1.70]) 21 years after implantation of 28 mm Metasul bearing, which was not significantly different from that at 5 years (0.70 µg/L [IQR, 0.2–1.8]).38 In this study, serum Co ion levels at ≥15 years were
also as low as those at <5 years although serum Cr ion levels were significantly higher (Table 3). Note that the Co ion level peaked at 5–10 years, which was significantly higher than that at <5 years, but it decreased to the initial level after 15 years. Alternatively, Cr ion levels increased significantly at 5–10 years and remained almost constant. This trend should reflect a time-dependent change in the balance between ion release from the device and ion excretion or storage (or potential consumption for tissue reactions)\(^{28,29}\). Renal excretion is the primary clearance mode of Co and Cr ions, but the kidney reportedly eliminates Co ions at a higher rate compared with Cr ions\(^{28,29}\). Furthermore, Cr ions bind more readily to proteins than Co ions, allowing Cr accumulation in local soft tissues and precipitation as chromium orthophosphate\(^{39}\). In these contexts, Cr ions might last longer in vivo than Co ions, suggesting the potential of Cr ion level as a more stable indicator. According to the current guideline\(^{40}\), serum Co and Cr ion levels of <2.0 \(\mu\)g/L are of no clinical concern. Possible biological effects of high Cr ion levels are DNA and chromosomal damage, reduction in CD8\(^+\) lymphocyte levels, and ARMD, although these effects remain controversial\(^{41}\).

Besides the serum ion levels, the Co/Cr ratio is an informative parameter to understand the long-term behavior of the released metal ions in the serum. The Co/Cr ratio of the base material within the ASTM guidelines ranges from 1.9 to 2.6 depending on the exact composition of the alloy used by the manufacturer\(^{42}\). Numerous studies\(^{19–21,43–45}\) have reported that, in large-head MoM THA, ARMD onset is associated with mechanically assisted (fretting) corrosion at the head–neck interfaces and its related metal ion release. The fretting corrosion is an irreversible interfacial reaction of material, often resulting in an active metal ion release. Under such circumstances, ion release might continuously occur at a faster rate than excretion and tissue reaction, increasing serum Co levels and the Co/Cr ratio in large-head MoM components being susceptible to large frictional torque at the modular head–neck interfaces\(^{19–21}\). Nevertheless, the fact that our results obtained from the small-head MoM THA did not follow the previously reported trend is interesting. The median Co/Cr ratio (5.0 [IQR, 4.8–7.3]) was highest within the first 5 years after THA, a value higher than that of the base material, and then decreased thereafter (Table 3, Fig. 2C). In fact, no obvious fretting corrosion was intraoperatively confirmed in the three ARMD patients during the revision surgeries, which might be due to less frictional torque at the head–neck junction associated with the use of the small-head bearings\(^{17}\). Thus, in our cases, articulating surfaces were probably a primary source of metal ion release rather than the head–neck interfaces. Because the wear rates of Metasul MoM articulation decreased with implantation time\(^{46}\), the Co/Cr ratio peaked within the first 5 years possibly due to the initial wear and then decreased possibly due to the reduced wear rate and increased ion excretion (primarily Co ion) and/or tissue reaction.

The overall trend of the Co/Cr ratio can be associated with the difference in ion release–excretion behavior between Co and Cr (i.e. a faster excretion of Co than Cr ion). Renner et al.\(^{47}\) have reported that Co/Cr ratios above 1.71 were predictive of osteolysis; however, ARMD was not studied as an
outcome. In our study on small-head Metasul bearings, most ARMD patients had Co/Cr ratios below 1.71 and a lower median Co/Cr ratio than non-ARMD patients. In fact, Fehring et al. have highlighted that the interplay between ion release and excretion makes the use of this ratio difficult as a diagnostic tool. Nevertheless, in our cases, the Co/Cr ratio succeeded in obtaining the statistical significances between non-ARM and ARMD patients after long-term follow-up (Table 4, Fig. 5). Thus, compared with the initial Co/Cr ratio at <5 years, its significant decrease might be associated with an increased risk of ARMD after small-head MoM THA. Additionally, the Co/Cr ratio may be a more sensitive predictor than serum Co levels alone, showing no significance at ≥15 years. These results suggest that, in small-head MoM THA, monitoring both Co and Cr ion levels is important for a more stable prediction of the ARMD risk.

Limitations of the Study

This study had the following limitations. First, the number of patients followed up over 15 years was relatively small (35 patients). Second, the infection rate was relatively high (Table 2), contributing to the reduced overall survival rate of the patients implanted with Metasul bearings. MoM bearings have been noted to be associated with a higher risk of periprosthetic infection than metal-on-polyethylene and ceramic-on-ceramic bearings. However, in the patients with infections in this study, the serum Co and Cr levels at the time of infection onset (within 5–6 years) remained below the level of clinical concern (<2.0 μg/L). All three revision cases due to infection were at high risk of infection; two cases of idiopathic osteonecrosis of the femoral head (Cases 1 and 2 in Table 2) were on high-dose steroids, and the other case of osteoarthritis (Case 4 in Table 2) was complicated with severe diabetes mellitus. Thus, metal ions released from Metasul bearings are unlikely to be associated with infection.

Conclusion

The risk of ARMD-related revision surgery significantly increased following MoM THA using 28 mm Metasul bearings beyond the postoperative period of 15 years. The long-term in vivo behavior differs between Co and Cr, and increased Cr ion levels and decreased Co/Cr ratio may be signs of ARMD. Our results suggest that careful screening is needed not only for large-head MoM patients but also for small-head MoM patients according to metal ion levels and clinical imaging findings.

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Ethics Approval and Consent to Participate

The institutional review board of our hospital approved this study.

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