Modular implant design affects metal ion release following metal-on-metal hip arthroplasty: a retrospective study on 75 cases

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Summary

Introduction: Metal-on-Metal (MoM) total hip arthroplasty (THA) has been associated to wear and metal-ions release, controversially related to a variety of clinical complications. Little is known about the relevant design-dependent parameters involved in this process. The present study investigated the correlation between metal ion release in blood and revision rate as a function of: (i) specific MoM implant modular design parameters, (i.e. acetabular cup and femoral head diameters, taper adapter material and size, femoral neck material and modularity and stem size); (ii) MoM bilaterality.

Methods: Co and Cr ions concentration levels in blood of 75 patients were retrospectively-evaluated with a mean follow-up of 4.8 years (range: 1.8–6.3). Patients were divided in a unilateral and a bilateral group. Statistical analysis was performed to find any significant difference related to acetabular cup diameter, femoral head diameter, taper adapter material/size, neck material/size and stem size.

Results: The bilateral MoM group had 4-times higher metal ion levels in blood than the unilateral one ($p=0.017$ only Cr), related to a higher revision rate (30% vs 20%): differences were 10-times higher particularly with a 48 mm femoral head diameter ($p=0.012$) and a Ti-alloy neck ($p=0.041$). Within the monolateral group using a shorter taper adapter and a shorter neutrally-oriented neck demonstrated higher ion levels ($p=0.038$ only Cr and $p=0.008$ only Co, respectively).

Conclusion: The aforementioned design-features and MoM bilaterality are important risk-factors for metal-ion release in modular MoM THA.

Keywords: Modular hip prosthesis; Metal-on-Metal; Metal ion release; Cobalt; Chromium; Revision; Metallosis.

Introduction

Total hip arthroplasty (THA) faced an innovation in the last two decades mainly related to the exploitation of modularity, potentially adapting to any peculiarity in patients' anatomy, and the introduction of new metal-on-metal (MoM) bearing surfaces, aimed at minimizing wear debris formation compared to conventional metal-on-polyethylene (MoP) couplings (1,2).

Recent clinical experience highlighted new potential issues related to the release of metallic ions and the formation of corrosion products leading to many complications. Adverse Local Tissue Reaction (ALTR), osteolysis and pseudotumour formation have often been reported as a consequence of metal-ion release in presence of large (diameter ≥36mm) MoM THA for a variety of implant designs (3–8). However, it must be recognized that no clear cause-effect relation has ever been quantitatively demonstrated (5). Moreover, some authors put under discussion the utility of metal ion levels detection alone as a reliable predictor of periarticular tissue reaction even in symptomatic patients (9,10). Clinical evidence pushed several national and international bodies to draw precautionary recommendations on the management and monitoring of metal ions levels in THA, particularly when MoM surface-bearings are used (caution range 2–7 µg/l, critical threshold 20 µg/l for Co) (11,12).

Despite controversial results not always leading to painful symptoms may suggest the involvement of specific biological factors (13,14) other never-investigated design-dependent parameters (i.e. implant size and materials) are expected to play a significant role.

The aim of the present retrospective comparative study is, therefore, to investigate the correlation between metal ions release in blood and (i) specific MoM implant modular design parameters, (i.e. acetabular cup and femoral head diameters, taper adapter material and size, femoral neck material and modularity and stem size), and (ii) MoM bilaterality.

Materials and Methods

Patients cohort

75 subjects (51 males, 24 females), implanted with at least one primary MoM THA between March 2008 and December 2011, have been retrospectively analyzed. All patients provided written signature on informed consent. Indication for surgery was justified by one of the following reasons: coxarthrosis, rheumatoid arthritis or avascular necrosis. Patients were divided in two groups. The first one received a unilateral MoM THA (monolateral group). The second one underwent a staged-bilateral MoM THA (bilateral group). All surgeries were performed via a posterolateral approach, the piriformis and conjoined tendons and the posterior capsule were repaired in separate layers using a transosseous technique. All patients involved in the study signed the informed consent for the treatment of their data.

Implants

All patients were implanted with at least one THA composed by a Harmony modular cementless femoral hip stem (Symbios Orthopédie SA, Yverdon-Les-Bains, Switzerland), a modular neck in Ti6Al4V or CoCrMo alloys coupled to a MaxiMoM taper adapter in CoCrMo or Ti6Al4V alloys, respectively, and a MaxiMoM femoral head-cup system (Symbios Orthopédie SA, Yverdon-Les-Bains, Switzerland) with a large diameter MoM CoCrMo couple bearing.

The femoral stems ranged between 9 and 16 in size. The neck length was classified according to the manufacturer as short and long. The taper adapters were classified according to the manufacturer depending on their size small (S), medium (M), large (L) and extra-large (XL). The femoral head and the monoblock cup diameters ranged in between 40 and 56mm and 48 to 64mm, respectively.

Metal ion level-measurements

Patients were retrospectively assessed for postoperative cobalt and chromium ions level in venous blood. All patients with a MoM implant underwent blood metal ion determination as part of a monitoring program at our institution. Recorded analyses were extracted directly from IRCCS Galeazzi Orthopaedic Institute database.

Co and Cr ions concentration levels were expressed in µg/l. Data were organized for each of the two groups and within each group as a function of the design feature of interest, namely: acetabular cup diameter, femoral head diameter, taper adapter material and size, neck material and size, stem size.

Clinical evaluation and Imaging

Patients routinely received a radiograph (X-ray) to confirm a correct implant positioning and osseointegration. Each patient was periodically followed by an attending physician, who performed a physical evaluation of any symptoms (e.g. pain, functional impairment). Further metal-ion analysis in blood and/or diagnostic imaging analysis were requested in some cases. Extra-routine radiographic analysis was further requested to check for suspected images of osteolytic areas around the implant or loosening. According to international consensus (11,12), specific symptomatic patients underwent extra-routine nuclear Magnetic Resonance Imaging (MRI), using a Metal Artifact Reduction Sequence (MARS) protocol, to look for the presence of cystic/solid soft tissue masses.

In specific cases, the attending physician decided for a revision surgery upon careful evaluation of all acquired information.

Statistical analysis

Statistical analyses were carried out with IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, Illinois). Preliminary multilinear regressions were undertaken to evaluate the relationship of Co and Cr ions levels to time and other specific design-features. A logarithm was necessary to transform the asymmetric metal ion distributions to approximately normal distributions (16, 17), as confirmed by Shapiro-Wilk normality test. Student's t-test was used to compare unilateral and bilateral MoM patients' groups and subgroups for metal levels assuming a significance level of 95% ($p<0.05$). Metal ion levels were presented as box-plot whenever possible (number of samples ≥ 3), specific values were reported otherwise.

To keep consistency, only patients with complete metal ion levels data are discussed herein against X-rays and MRI imaging analysis. The revision rate was reported in terms of absolute (over the whole population) and relative (for each patients' group) frequency. No attempt was made to quantitatively correlate metal ion levels with positive MRIs, X-rays nor symptoms.

Results

Patients cohort

65 patients (86.7%) received a unilateral MoM THA (monolateral group) with a male-female ratio of 42:23 (demographic data are summarized in Table 1). 2 patients within the monolateral group had a non-MoM THA with a monolithic femoral component on the contralateral side.

10 patients (13.3%) received a staged-bilateral MoM THA (bilateral group) with a male:female ratio of 9:1. Only one patient had a Profemur Z femoral stem with modular neck, both in Ti6Al4V alloy, a CoCrMo taper adapter, a CoCrMo femoral head coupled

to a Procotyl acetabular (all components by Wright Medical Technology, Inc., Arlington, TN)

Metal ion level-measurements

Complete data were collected for 45 patients (60% of all patients) (Table 2): 38 in unilateral group (male:female ratio of 27:11), 7 in bilateral group (6:1). 19 patients (25.3%) presented incomplete or not-available data, while the remaining 11 (14.7%) were lost at follow-up.

The metal ion level analysis was repeated over time for 15 patient; the average value was considered in the subsequent analysis since no correlation was observed over time.

The linear regression analysis demonstrates a very weak correlation between metal ions concentrations and acetabular cup diameter, femoral head diameter and stem size for each patients' group.

In general, the bilateral MoM group (Co: 44.9±42.7µg/l; Cr: 23.0±21.4µg/l) exhibited 4-fold higher metal ion levels in blood than the unilateral one (Co: 10.0±7.5µg/l; Cr: 4.5±3.6µg/l), however they resulted significant only for Cr (p=0.017) (Table 2, Figure 1).

As regards intergroup comparison, we found significantly higher Cr levels in bilateral group than in unilateral one with a 48mm head diameter (respectively, 43.2±32.8µg/l vs. 2.3±0.8 µg/l, p=0.012; Figure 1), as well as with a Ti6Al4V neck material (respectively, 42.6±33.1µg/l vs. 3.5±2.2µg/l, p=0.041; Figure 3). Despite the trend is similar, no statistical difference was met for Co.

About unilateral intragroup comparison, we found significantly higher Cr and Co levels, respectively, with a short (S) taper adapter size than a medium (M) (respectively, 9.9±7.1µg/l vs. 2.4±1.2µg/l, p=0.038; Figure 2) and with a shorter neutrally-oriented neck size instead of a longer (23.5±15.8 µg/l vs. 3.5±1.6 µg/l, p=0.008; Figure 3).

No further significant differences were detected within each group nor among them considering cup diameter, taper adapter material (Figure 2), nor stem size (Figure 4) within the monolateral group.

Clinical evaluation and Imaging

In 37/75 patients (49% of total population) a further radiographic analysis was requested (Table 1). Clear osteolytic areas and implant mobilization were positively assessed in 13 of them (17% of all patients): incidence was 2-fold higher in the bilateral group compared to the monolateral one (respectively, 4/10 vs. 9/65).

30 patients (40% of total population) underwent an MRI, eventually according to an enhanced MARS protocol (Table 1), confirming the presence of cystic/solid soft tissue masses in 23 cases (31% of all patients): again, the incidence was 2-times higher for the bilateral group compared to the monolateral (respectively, 5/10 vs. 18/65).

When considering only patients with complete metal-ions level data, the relative incidence of positive RXs and MRIs confirmed to be about 2-times higher for the bilateral MoM group than the monolateral (Table 2).

Revision

16 patients (21% of total population) underwent revision surgery at an average postoperative time of 3.5±1.1 years (Tables 1,2). In all revised cases, a ceramic head (Biolox Delta) was coupled to highly-cross-linked-polyethylene (XLPE) upon revision. Revision surgery due to sepsis was performed in 2 patients following a two-stage procedure with an antibiotic-loaded spacer.

The absolute revision rate was higher for the bilateral group (30%), but the sample size was different (13/65 vs. 3/10, respectively). All revised patients reported symptoms (i.e. pain, functional impairment), sometimes confirmed through X-rays or MRI imaging analysis (Supplementary Material 1,2).

Considering only patients with complete metal-ions level data (Table 2), the relative frequency of revision was slightly lower (16%), but similar for both groups (bilateral: 2/7 vs. monolateral: 5/38).

In general, all revised patients (Co: 54.3±45.2 µg/l; Cr: 30.0±23.0 µg/l) demonstrated significantly higher (Co: $p=0.014$, Cr: $p=0.011$) metal ion levels in blood than those unrevised (Co: 15.2±18.0 µg/l; Cr: 7.4±9.2 µg/l) (Table 2). It is important to notice that such a result was not confirmed by a statistical difference between revised and unrevised patients within the monolateral group (Co: $p=0.104$, Cr: $p=0.060$).

Among the 7 revised patients with complete metal-ion level data (Supplementary Material 2), 5 had a positive MRI: 2 patients overcame the threshold of 20 µg/l for Co, while 2 were beyond the caution range for Co (2–7 µg/l). Despite the 2 remaining patients were in the caution range, both of them were revised due to implant loosening, but in one case a prosthetic joint infection (PJI) was the leading cause.

Discussion

In the present study, we considered a large-head MoM THA design (femoral head diameters: 40–56 mm), based on modular parts differing in size and material, which has never been considered in the previous literature. Even considering only the unilateral group (the only with enough samples), we noticed a slight trend toward higher average metal ion levels and higher absolute number of revisions with lower femoral head diameters (Figure 1): 8 cases of revision at 44 mm, 3 at 40 mm and only 2 at 48 mm. Being femoral head diameter and acetabular cup size roughly proportional, the same trend could be discussed also for the latter parameter. Neglecting isolated peak values, the highest average metal ions concentrations were met at 44 mm for each of the two groups, without any significant difference compared to other diameters. A large systematic review reported highest metal ion concentrations after treatment with stemmed large-head MoM-implants and hip resurfacing arthroplasty(5), particularly in female gender (15). Beaulé and colleagues demonstrated that large-head MoM THA had significantly-higher Co level at 6-month, not confirmed for Cr, compared to hip-resurfacing system (16).

A pattern similar to the one we reported, with trend for ions concentration decreasing as bearing diameter increased, has been already showed for large-diameters THA (>55 mm) and hip resurfacing systems (17). Conversely, significantly higher Co levels for larger-head diameters (≥50 mm) compared to relatively-smaller head (range: 42–48 mm) in modular THA were also reported (8). The explanation for higher metal ion release in smaller diameters should be searched in the reduced arcs of cover and the predisposition to edge wear of these components. On the other hand the open design of larger femoral heads (≥50 mm) with a larger contact surface for metal corrosion can account for higher metal ion levels compared to the closed head designs (≤48 mm).

Despite the debate is still open, international consensus-based statements on ions levels in blood have been defined: the threshold value for clinical concern is expected to be within the range of 2–7 µg/l, whereas excessive elevation (Co approximately 20g/L or above) of metal ions should prompt discussion with the patient about revision surgery because of potential osteolysis, tissue necrosis, and long-term health effects (11,12). Moreover, the current recommendation is to support metal ion level evaluation with specific imaging techniques (e.g. ultrasound, MARS-MRI, CT Scan,) and a systematic follow-up on patients implanted with a MoM bearing .

Beside femoral head diameters, other design-parameters needs further discussion against metal ion release. In fact, modular MoM THA designs often have several interfaces undergoing micromotions and susceptible of wear debris formation.

Vendittoli demonstrated that the addition of a taper adapter with modular junctions and an open femoral head design causes more Co release than bearing surface wear in modular large-head MoM THA (8). Moreover, little is known on the consequences of using modular femoral necks and taper adapter with a variety of sizes and/or materials. To the best of our knowledge, these aspects received very little attention in the literature.

As for implant modularity, the data collected for the unilateral group demonstrated significantly higher Cr levels using a shorter taper adapter size, while we noticed only a trend towards increased metal ion release with a Ti6Al4V taper adapter: in both cases this result is associated to a higher revision rate (Figure 2). Despite only Co levels are significantly higher using a smaller neck instead of a long one (Figure 3), we noticed a trend towards a slightly higher revision rate (7/65 vs. 6/65, respectively); even though the average ion levels are similar, a femoral neck in CoCr is however related to a higher number of revision compared to Ti6Al4V (Figure 3). These results may suggest that the modularity of neck- taper adapter system play an important role. In particular, increasing the bending stiffness of the neck-taper system (i.e. shorter/stiffer CoCr neck + shorter adapter size), may promote wear on the taper adapter, which would work as a damper interposed in-between the neck and the head taper joint. This mechanism may be promoted especially with a softer Ti6Al4V taper adapter with a reduced thickness (i.e. small size). To the best of our knowledge, only one recent radiographic study seemed to confirm our results towards an increased risk of complication (i.e. pseudotumour formation) in the long-term when a titanium taper adapter is used (18).

As concern MoM bilaterality, we found that, in general, having a bilateral MoM THA led to higher Co and Cr values compared to the unilateral group, but they were significant only for Cr. Interestingly, Witzleb reported the same results for a THA with a smaller (28 mm) diameter until 1 year, but thereafter they did not notice any difference (19). Pelt found slightly higher cobalt levels in well-functioning MOM THA, not in chromium (20), while other study did not notice any difference (21). However, the difference we observed in metal-ions level found a confirmation in the absolute revision rate, which was higher for the bilateral group (3/10 or 30%) compared to the monolateral one (13/65 or 20%). Other studies including a variety of modular MoM THA designs reported variable revision rates: Bernthal found a 17% (or 12/70) for ultra-large-diameter femoral heads paired with a monoblock acetabular cup (22), while Mauer-Ertl reported a 27% (or 12/44) for large-head articular surface replacement systems (44-58mm) (23); Langton obtained a 6% (or 5/87) (24) and a 49% (or 42/87) (17) for large-head diameters THA (39-57mm and >55mm, respectively), whilst Koziara reported a 22% (or 21/66) (25).

The current retrospective study presents some intrinsic limitations. Information about the preoperative ion-concentration levels is missing. Data were not acquired at regular follow-up times, nor they were homogeneously distributed across the two groups. The limited sample size made, sometimes, impossible to perform any quantitative statistical analysis. This aspect was more critical for the bilateral MoM group, where different implant size and material were mixing up adding a confounding effect. Moreover, issues related to the ion level evaluation (9,10), resulted in very highly-dispersed data, with rather high and isolated values.

The paper related modular design features of MoM THA to significant differences in Co and Cr levels in blood: neck length and taper adapter size were found to contribute in increasing metal-ion release.

Having a bilateral MoM THA may lead to higher absolute metal-ion levels in blood compared to a unilateral implant, however the revision rate is comparable.

Complete diagnostic imaging analysis and a rigorous clinical evaluation of patients, represent necessary information to integrate metal ion level measurements and to support physicians in decision-making process.

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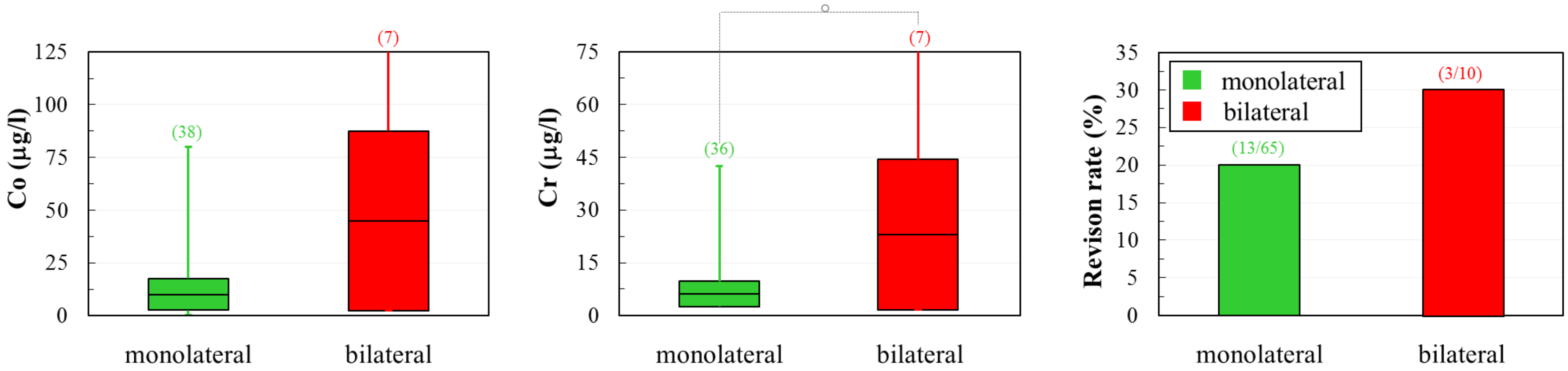

Figure 1: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) for monolateral and bilateral MoM groups.

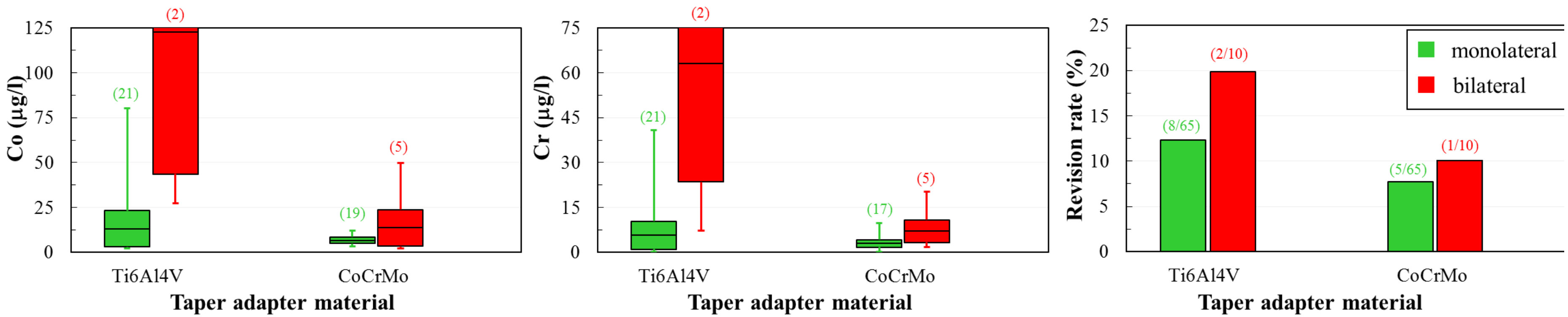

Figure 2: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of taper adapter material. Statistically significant differences are indicated (*: $p<0.05$).

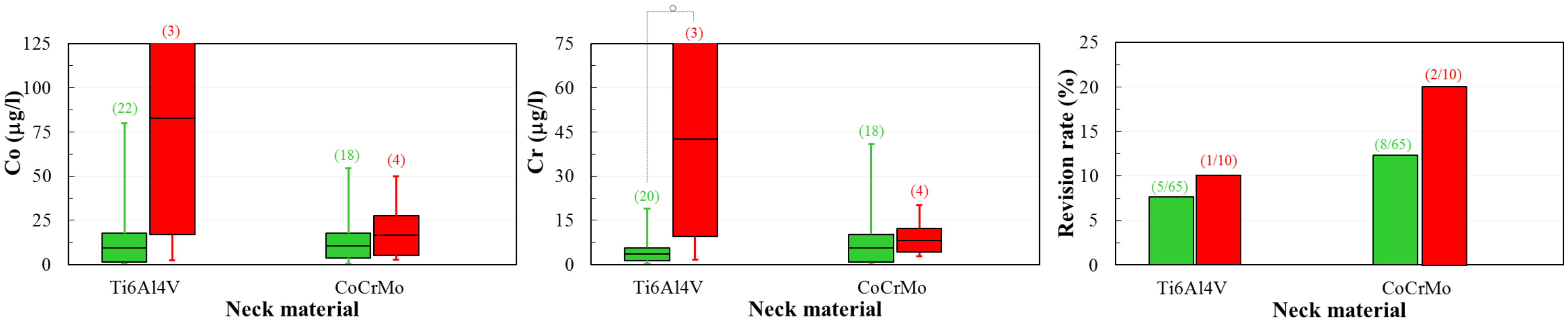

Figure 3: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of femoral neck material. Statistically significant differences are indicated (* or °: $p<0.05$).

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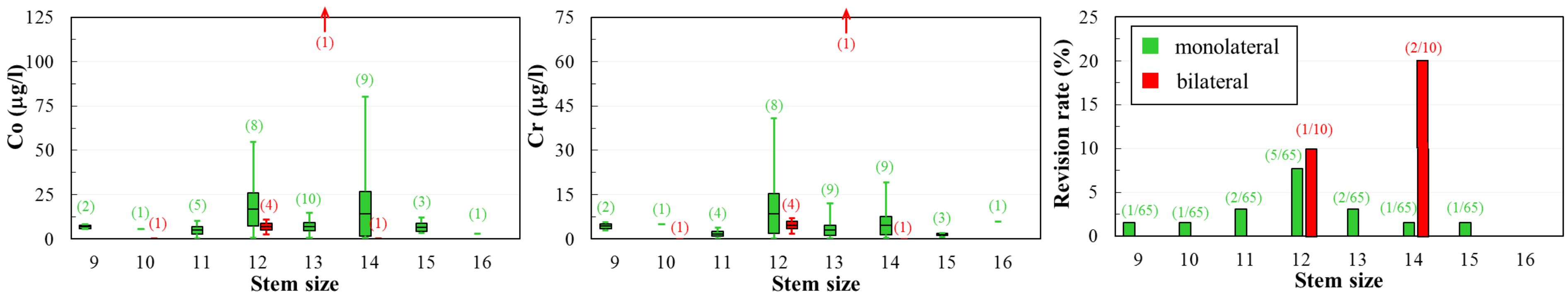

Figure 4: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of stem size.

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Table 1: General demographic information for each patients' group and the overall population.

	Monolateral group	**Bilateral MoM group**	**All patients**
Patients' population (#)	**65 (42:23)**	**10 (9:1)**	**75 (51:24)**
Age at first surgery (years) mean ± standard dev. (min – max)	58.2 ± 11.1 (22.2 – 75.7)	56.2 ± 9.7 (38.6 – 72.7)	57.9 ± 10.9 (22.0 – 75.7)
Age at second surgery (years)	-	0.8 ± 0.8 (0.0 – 2.6)	-
Lost patients at follow-up (#)	**11**	**0**	**11**
(%)	16.9%	-	14.7%
Patients with incomplete or not available data (#)	**16**	**3**	**19**
(%)	24.6%	30.0%	25.3%
Number of patients with complete ions level data (male:female)	**38 (27:11)**	**7 (6:1)**	**45 (33:12)**
(% of total population) (male : female)	58.5% (64.3 : 47.8)	70.0% (66.7 : 100)	60.0% (64.7 : 50.0)
Follow-up time (years)	4.0 ± 0.4 (3.1 – 6.4)	4.1 ± 0.5 (2.7 – 6.0)	4.0 ± 0.4 (2.7 – 6.4)
Patients with extra-routine RX analysis (#)	**29**	**8**	**37**
(% of total population)	44.6%	80.0%	49.3%
Positive extra-routine RX analysis (#)	**9**	**5**	**14**
(% of total population)	13.8%	50.0%	18.7%
Patients with extra-routine MRI (conventional / MARS) analysis (#)	**23 (7 / 16)**	**7 (3 / 4)**	**30 (10 / 20)**
(% of total population)	35.4% (10.8 / 24.6)	70% (30 / 40)	40% (13.3 / 26.7)
Patients with positive extra-routine MRI (conventional / MARS) analysis (#)	**18 (6 / 12)**	**5 (2 / 3)**	**23 (8 / 15)**
(% of total population)	27.7% (9.2 / 18.5)	50% (20 / 30)	30.7% (10.7 / 20.0)
Number of revised patients (#) (male:female)	**13 (7:6)**	**3 (2:1)**	**16 (9:7)**
(%) (male : female)	20.0% (16.7 : 6.1)	30.0% (22.2 : 100)	21.3% (17.7 : 29.2)
Age at revision (years) (male:female)	3.4 ± 1.1 (1.7 – 4.8)	5.0 ± 2.1 (2.8 – 7.0)	3.7 ± 1.4 (1.7 – 7.0)

Table 2: Demographic information for patients with complete metal-ions level data.
*: Significant difference compared to the monolateral group ($p<0.05$).

	Monolateral group	**Bilateral MoM group**	**All patients**
Patients with complete Co-level data (#)	**38 (27:11)**	**7 (6:1)**	**45 (33:12)**
(% of total population)	58.5% (64.3 : 47.8)	70% (66.7 : 100)	60% (64.7 : 50)
Follow-up time (years)	4.0 ± 0.4 (3.1 – 6.4)	4.1 ± 0.5 (2.7 – 6.0)	4.0 ± 0.4 (2.7 – 6.4)
Co ion level (µg/l)	10.0 ± 7.5 (0.3 – 80.1)	44.9 ± 42.7 (2.5 – 234.8)	15.2 ± 18.0 (0.3 – 234.8)
Cr ion level (µg/l)	4.5 ± 3.6 (0.1 – 40.8)	23.0 ± 21.4 (1.7 – 119.0) *	7.4 ± 9.2 (0.1– 119.0)
Patients with Co < 2 µg/l (#)	**9**	**0**	**9**
(% of patients with complete ion level data)	23.7%	- %	20%
Patients with Co in the range 2–7 µg/l (#)	**12**	**4**	**16**
(% of patients with complete ion level data)	31.6%	57.1%	35.6%
Patients with Co in the range 7–20 µg/l (#)	**16**	**1**	**17**
(% of patients with complete ion level data)	42.1%	14.3%	37.8%
Patients with Co >20 µg/l (#)	**3**	**2**	**5**
(% of patients with complete ion level data)	7.9%	28.6%	11.1%
Patients with extra-routine RX analysis (#)	**17**	**6**	**23**
(% of patients with complete ion level data)	44.7%	85.7%	51.1%
Patients with positive extra-routine RX analysis (#)	**5**	**2**	**7**
(% of patients with complete ion level data)	13.1%	28.6%	15.6%
Patients with extra-routine MRI (conventional / MARS) analysis (#)	**17 (5 / 12)**	**5 (2 / 3)**	**22 (7 / 15)**
(% of patients with complete ion level data)	44.7% (13.1 / 31.6)	71.4% (28.6 / 42.9)	48.9% (15.6 / 33.3)
Patients with positive extra-routine MRI (conventional / MARS) analysis (#)	**12 (4 / 8)**	**4 (1 / 3)**	**16 (5 / 11)**
(% of patients with complete ion level data)	31.6% (10.5 / 21.1)	57.1% (14.3 / 42.9)	35.6% (11.1 / 24.4)
Number of revised patients (#)	**5 (3:2)**	**2 (1:1)**	**7 (4:3)**
(% of patients with complete ion level data) (male : female)	13.2% (11.1 : 18.2)	28.6% (16.7 : 100)	15.6% (12.1 : 25.0)
(% of total population) (male : female)	7.8% (7.1 : 8.7)	20% (10.0 : 10.0)	9.3% (7.8 : 12.5)
Follow-up time (years)	3.5 ± 0.2 (3.1– 4.2)	3.9 ± 0.8 (3.3 – 4.5)	3.6 ± 0.3 (3.1 – 4.5)
Co ion level (µg/l)	18.2 ± 10.4 (3.8 – 54.7)	155 ± 148 (49 – 260)	54.3 ± 45.2 (3.8 – 260)
Cr ion level (µg/l)	12.2 ± 8.3 (1.3 – 40.8)	69.6 ± 69.9 (20.1 – 119)	30.0 ± 23.0 (1.3 – 119.0)

Supplementary Material 1: Diagnostic information for revised patients with incomplete/not available metal-ions level data and diagnostic imaging information (n.a.: not available; x: positive; o: negative; -: not done).

Patient	Co level (μg/l)	Cr level (μg/l)	RX	RMI	Symptoms (pain, functional impairment)	Suggested Diagnosis
M-20	100	n.a.	o	x	x	Metallosis
M-19	10.3	1.3	o	x	x	Metallosis
M-21	x	x	x	x	x	Metallosis
M-3	x	x	x	o	x	Cup mobilization
M-26	n.a.	n.a.	x	x	n.a.	Metallosis
M-23	n.a.	n.a.	x	x	x	Metallosis
M-25	n.a.	n.a.	x	-	x	Sepsis (Stapph.Epiderm.)
M-24	n.a.	n.a.	x	-	x	Cup mobilization
M-22	o	o	o	-	x	Stem mobilization

Supplementary Material 2: Diagnostic information for revised patients with complete metal-ions level data and diagnostic imaging information (x: positive; o: negative; -: not done).

Patient	Co level (μg/l)	Cr level (μg/l)	RX	RMI	Symptoms (pain, functional impairment)	Suggested Diagnosis
B-8	234.8	119.0	o	x	x	Metallosis
M-16	54.7	40.8	-	x	x	Metallosis
B-5	49.9	20.1	x	-	x	Stem mobilization
M-18	14.7	12.0	o	x	x	Stem mobilization
M-36	12.2	1.8	-	x	x	Periarticular cysts
M-17	5.8	5.1	x	x	x	Stem mobilization
M-12	3.8	1.3	x	-	x	Sepsis, stem/cup loosening