

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

3 La Barbera L¹, D’Apolito R², Peretti GM^{2,3}, Piergiovanni M¹, Banfi G², Zagra L²

4
5 1: Laboratory of Biological Structure Mechanics, Department of Chemistry, Materials
6 and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Piazza Leonardo
7 da Vinci 32, 20133 Milan, Italy

8 2: IRCCS Istituto Ortopedico Galeazzi, Milan, via Riccardo Galeazzi 4, 20161 Milan,
9 Italy

10 3: Department of Biomedical Sciences for Health, University of Milan, 20122 Milan,
11 Italy

12
13
14 **Corresponding author:**

15 Luigi Zagra

16 IRCCS Istituto Ortopedico Galeazzi

17 Via R. Galeazzi 4, 20161, Milan, Italy

18 Office: Tel.: +39 02 6621 4734

19 E-mail: rolp.dir@libero.it or luigi.zagra@fastwebnet.it

20

21 **Summary**

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

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

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

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

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

44 **Introduction**

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

50 Recent clinical experience highlighted new potential issues related to the release of
51 metallic ions and the formation of corrosion products leading to many complications.
52 Adverse Local Tissue Reaction (ALTR), osteolysis and pseudotumour formation have
53 often been reported as a consequence of metal-ion release in presence of large (diameter
54 ≥ 36 mm) MoM THA for a variety of implant designs (3–8). However, it must be
55 recognized that no clear cause-effect relation has ever been quantitatively demonstrated
56 (5). Moreover, some authors put under discussion the utility of metal ion levels
57 detection alone as a reliable predictor of periarticular tissue reaction even in
58 symptomatic patients (9,10). Clinical evidence pushed several national and international
59 bodies to draw precautionary recommendations on the management and monitoring of
60 metal ions levels in THA, particularly when MoM surface-bearings are used (caution
61 range 2–7 $\mu\text{g/l}$, critical threshold 20 $\mu\text{g/l}$ for Co) (11,12).

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

66 The aim of the present retrospective comparative study is, therefore, to investigate the
67 correlation between metal ions release in blood and (i) specific MoM implant modular
68 design parameters, (i.e. acetabular cup and femoral head diameters, taper adapter

69 material and size, femoral neck material and modularity and stem size), and (ii) MoM
70 bilaterality.

71

72 **Materials and Methods**

73 Patients cohort

74 75 subjects (51 males, 24 females), implanted with at least one primary MoM THA
75 between March 2008 and December 2011, have been retrospectively analyzed. All
76 patients provided written signature on informed consent. Indication for surgery was
77 justified by one of the following reasons: coxarthrosis, rheumatoid arthritis or avascular
78 necrosis. Patients were divided in two groups. The first one received a unilateral MoM
79 THA (monolateral group). The second one underwent a staged-bilateral MoM THA
80 (bilateral group). All surgeries were performed via a posterolateral approach, the
81 piriformis and conjoined tendons and the posterior capsule were repaired in separate
82 layers using a transosseous technique. All patients involved in the study signed the
83 informed consent for the treatment of their data.

84 Implants

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

91 The femoral stems ranged between 9 and 16 in size. The neck length was classified
92 according to the manufacturer as short and long. The taper adapters were classified
93 according to the manufacturer depending on their size small (S), medium (M), large (L)

94 and extra-large (XL). The femoral head and the monoblock cup diameters ranged in
95 between 40 and 56mm and 48 to 64mm, respectively.

96 Metal ion level-measurements

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

101 Co and Cr ions concentration levels were expressed in $\mu\text{g/l}$. Data were organized for
102 each of the two groups and within each group as a function of the design feature of
103 interest, namely: acetabular cup diameter, femoral head diameter, taper adapter material
104 and size, neck material and size, stem size.

105 Clinical evaluation and Imaging

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

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

118 Statistical analysis

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

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

133

134 **Results**

135 Patients cohort

136 65 patients (86.7%) received a unilateral MoM THA (monolateral group) with a male-
137 female ratio of 42:23 (demographic data are summarized in Table 1). 2 patients within
138 the monolateral group had a non-MoM THA with a monolithic femoral component on
139 the contralateral side.

140 10 patients (13.3%) received a staged-bilateral MoM THA (bilateral group) with a
141 male:female ratio of 9:1. Only one patient had a Profemur Z femoral stem with modular
142 neck, both in Ti6Al4V alloy, a CoCrMo taper adapter, a CoCrMo femoral head coupled

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

145 Metal ion level-measurements

146 Complete data were collected for 45 patients (60% of all patients) (Table 2): 38 in
147 unilateral group (male:female ratio of 27:11), 7 in bilateral group (6:1). 19 patients
148 (25.3%) presented incomplete or not-available data, while the remaining 11 (14.7%)
149 were lost at follow-up.

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

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

155 In general, the bilateral MoM group (Co: $44.9 \pm 42.7 \mu\text{g/l}$; Cr: $23.0 \pm 21.4 \mu\text{g/l}$) exhibited
156 4-fold higher metal ion levels in blood than the unilateral one (Co: $10.0 \pm 7.5 \mu\text{g/l}$; Cr:
157 $4.5 \pm 3.6 \mu\text{g/l}$), however they resulted significant only for Cr ($p=0.017$) (Table 2, Figure
158 1).

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

164 About unilateral intragroup comparison, we found significantly higher Cr and Co levels,
165 respectively, with a short (S) taper adapter size than a medium (M) (respectively,
166 $9.9 \pm 7.1 \mu\text{g/l}$ vs. $2.4 \pm 1.2 \mu\text{g/l}$, $p=0.038$; Figure 2) and with a shorter neutrally-oriented
167 neck size instead of a longer ($23.5 \pm 15.8 \mu\text{g/l}$ vs. $3.5 \pm 1.6 \mu\text{g/l}$, $p=0.008$; Figure 3).

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

171 Clinical evaluation and Imaging

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

176 30 patients (40% of total population) underwent an MRI, eventually according to an
177 enhanced MARS protocol (Table 1), confirming the presence of cystic/solid soft tissue
178 masses in 23 cases (31% of all patients): again, the incidence was 2-times higher for the
179 bilateral group compared to the monolateral (respectively, 5/10 vs. 18/65).

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

183 Revision

184 16 patients (21% of total population) underwent revision surgery at an average
185 postoperative time of 3.5 ± 1.1 years (Tables 1,2). In all revised cases, a ceramic head
186 (BioloX Delta) was coupled to highly-cross-linked-polyethylene (XLPE) upon revision.
187 Revision surgery due to sepsis was performed in 2 patients following a two-stage
188 procedure with an antibiotic-loaded spacer.

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

193 Considering only patients with complete metal-ions level data (Table 2), the relative
194 frequency of revision was slightly lower (16%), but similar for both groups (bilateral:
195 2/7 vs. monolateral: 5/38).

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

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

206

207 **Discussion**

208 In the present study, we considered a large-head MoM THA design (femoral head
209 diameters: 40–56 mm), based on modular parts differing in size and material, which has
210 never been considered in the previous literature. Even considering only the unilateral
211 group (the only with enough samples), we noticed a slight trend toward higher average
212 metal ion levels and higher absolute number of revisions with lower femoral head
213 diameters (Figure 1): 8 cases of revision at 44 mm, 3 at 40 mm and only 2 at 48 mm.
214 Being femoral head diameter and acetabular cup size roughly proportional, the same
215 trend could be discussed also for the latter parameter. Neglecting isolated peak values,
216 the highest average metal ions concentrations were met at 44 mm for each of the two
217 groups, without any significant difference compared to other diameters. A large

218 systematic review reported highest metal ion concentrations after treatment with
219 stemmed large-head MoM-implants and hip resurfacing arthroplasty(5), particularly in
220 female gender (15). Beaulé and colleagues demonstrated that large-head MoM THA had
221 significantly-higher Co level at 6-month, not confirmed for Cr, compared to hip-
222 resurfacing system (16).

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

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

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

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

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

265 As concern MoM bilaterality, we found that, in general, having a bilateral MoM THA
266 led to higher Co and Cr values compared to the unilateral group, but they were
267 significant only for Cr. Interestingly, Witzleb reported the same results for a THA with

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

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

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

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

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

296

297 **Acknowledgments**

298 Dr. Giampietro Pasolini and Dr. Alfredo Falchi are acknowledged for patients' clinical
299 evaluation, surgery and revision.

300

301 **References**

- 302 (1) Amstutz HC, Grigoris P. Metal on metal bearings in hip arthroplasty. *Clin Orthop Relat Res*
303 1996. doi:10.1097/00003086-199608001-00003.
- 304 (2) Srinivasan A, Jung E, Levine BR. Modularity of the femoral component in total hip arthroplasty.
305 *J Am Acad Orthop Surg* 2012;20:214–22. doi:10.5435/JAAOS-20-04-214.
- 306 (3) Ricciardi BF, Nocon AA, Jerabek SA, Wilner G, Kaplowitz E, Goldring SR, et al.
307 Histopathological characterization of corrosion product associated adverse local tissue reaction in
308 hip implants: A study of 285 cases Histopathology. *BMC Clin Pathol* 2016;16.
309 doi:10.1186/s12907-016-0025-9.
- 310 (4) Babis GC, Stavropoulos NA, Sasalos G, Ochsenkuehn-Petropoulou M, Megas P. Metallosis and
311 elevated serum levels of tantalum following failed revision hip arthroplasty--a case report. *Acta*
312 *Orthop* 2014;85:677–80. doi:10.3109/17453674.2014.950816.
- 313 (5) Hartmann A, Hannemann F, Lützner J, Seidler A, Drexler H, Günther KP, et al. Metal Ion
314 Concentrations in Body Fluids after Implantation of Hip Replacements with Metal-on-Metal
315 Bearing - Systematic Review of Clinical and Epidemiological Studies. *PLoS One* 2013;8.
316 doi:10.1371/journal.pone.0070359.
- 317 (6) Levine BR, Hsu AR, Skipor AK, Hallab NJ, Paprosky WG, Galante JO, et al. Ten-Year Outcome
318 of Serum Metal Ion Levels After Primary Total Hip Arthroplasty. *J Bone Jt Surg* 2013;95:512–8.
319 doi:10.2106/JBJS.L.00471.
- 320 (7) Jantzen C, Jørgensen HL, Duus BR, Sporring SL, Lauritzen JB. Chromium and cobalt ion
321 concentrations in blood and serum following various types of metal-on-metal hip arthroplasties: A
322 literature overview. *Acta Orthop* 2013;84:229–36. doi:10.3109/17453674.2013.792034.
- 323 (8) Vendittoli PA, Amzica T, Roy AG, Lusignan D, Girard J, Lavigne M. Metal Ion Release With
324 Large-Diameter Metal-on-Metal Hip Arthroplasty. *J Arthroplasty* 2011;26:282–8.
325 doi:10.1016/j.arth.2009.12.013.
- 326 (9) Malek IA, King A, Sharma H, Malek S, Lyons K, Jones S, et al. The sensitivity, specificity and
327 predictive values of raised plasma metal ion levels in the diagnosis of adverse reaction to metal

- 328 debris in symptomatic patients with a metal-on-metal arthroplasty of the hip. *J Bone Joint Surg Br*
329 2012;94-B:1045–50. doi:10.1302/0301-620X.94B8.27626.
- 330 (10) Griffin WL, Fehring TK, Kudrna JC, Schmidt RH, Christie MJ, Odum SM, et al. Are metal ion
331 levels a useful trigger for surgical intervention? *J Arthroplasty* 2012;27:32–6.
332 doi:10.1016/j.arth.2012.03.020.
- 333 (11) Klaus-Peter G, Jochen S, Patricia C, Delaunay Christian P, Hans D, Ettema Harmen B, et al.
334 Consensus statement “Current evidence on the management of metal-on-metal bearings” April
335 16, 2012. *HIP Int* 2013;23:2–5. doi:10.5301/HIP.2013.10754.
- 336 (12) Hannemann F, Hartmann A, Schmitt J, Lützner J, Seidler A, Campbell P, et al. European
337 multidisciplinary consensus statement on the use and monitoring of metal-on-metal bearings for
338 total hip replacement and hip resurfacing. *Orthop Traumatol Surg Res* 2013;99:263–71.
339 doi:10.1016/j.otsr.2013.01.005.
- 340 (13) Paukkeri EL, Korhonen R, Hämäläinen M, Pesu M, Eskelinen A, Moilanen T, et al. The
341 inflammatory phenotype in failed metal-on-metal hip arthroplasty correlates with blood metal
342 concentrations. *PLoS One* 2016;11. doi:10.1371/journal.pone.0155121.
- 343 (14) Pijls BG, Meessen JMTA, Schoones JW, Fiocco M, Van Der Heide HJL, Sedrakyan A, et al.
344 Increased mortality in metal-on-metal versus non-metal-on-metal primary total hip arthroplasty at
345 10 years and longer follow-up: A systematic review and meta-analysis. *PLoS One* 2016;11.
346 doi:10.1371/journal.pone.0156051.
- 347 (15) Vendittoli P-A, Mottard S, Roy AG, Dupont C, Lavigne M. Chromium and cobalt ion release
348 following the Durom high carbon content, forged metal-on-metal surface replacement of the hip.
349 *J Bone Jt Surg - Br Vol* 2007;89-B:441–8. doi:10.1302/0301-620X.89B4.18054.
- 350 (16) Beaulé PE, Kim PR, Hamdi A, Fazekas A. A Prospective Metal Ion Study of Large-Head Metal-
351 on-Metal Bearing: A Matched-Pair Analysis of Hip Resurfacing Versus Total Hip Replacement.
352 *Orthop Clin North Am* 2011;42:251–7. doi:10.1016/j.ocl.2011.01.005.
- 353 (17) Langton DJ, Jameson SS, Joyce TJ, Gandhi JN, Sidaginamale R, Mereddy P, et al. Accelerating
354 failure rate of the ASR total hip replacement. *Bone Joint J* 2011;93-B:1011–6. doi:10.1302/0301-
355 620X.93B8.26040.
- 356 (18) Hjørth MH, Egund N, Mechlenburg I, Gelineck J, Jakobsen SS, Soballe K, et al. Does a titanium
357 sleeve reduce the frequency of pseudotumors in metal-on-metal total hip arthroplasty at 5–7 years
358 follow-up? *Rev Chir Orthop Traumatol* 2016;102:739. doi:10.1016/j.rcot.2016.09.030.
- 359 (19) Witzleb WC, Ziegler J, Krummenauer F, Neumeister V, Guenther KP. Exposure to chromium,
360 cobalt and molybdenum from metal-on-metal total hip replacement and hip resurfacing
361 arthroplasty. *Acta Orthop* 2006;77:697–705. doi:10.1080/17453670610012863.
- 362 (20) Pelt CE, Bergeson AG, Anderson LA, Stoddard GJ, Peters CL. Serum Metal Ion Concentrations
363 After Unilateral vs Bilateral Large-Head Metal-on-Metal Primary Total Hip Arthroplasty. *J*
364 *Arthroplasty* 2011;26:1494–500. doi:10.1016/j.arth.2011.03.037.
- 365 (21) Hur CI, Yoon TR, Cho SG, Song EK, Seon JK. Serum ion level after metal-on-metal THA in
366 patients with renal failure. *Clin Orthop Relat Res* 2008;466:696–9. doi:10.1007/s11999-007-
367 0093-3.

- 368 (22) Bernthal NM, Celestre PC, Stavrakis AI, Ludington JC, Oakes DA. Disappointing Short-Term
369 Results With the DePuy ASR XL Metal-on-Metal Total Hip Arthroplasty. *J Arthroplasty*
370 2012;27:539–44. doi:10.1016/j.arth.2011.08.022.
- 371 (23) Maurer-Ertl W, Friesenbichler J, Holzer LA, Leitner L, Ogris K, Maier M, et al. Recall of the
372 ASR XL Head and Hip Resurfacing Systems. *Orthopedics* 2017;40:e340–7.
373 doi:10.3928/01477447-20161213-04.
- 374 (24) Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natsu S, Nargol AVF. Early failure of metal-on-
375 metal bearings in hip resurfacing and large-diameter total hip replacement: A CONSEQUENCE
376 OF EXCESS WEAR. *J Bone Jt Surg - Br Vol* 2010;92–B:38–46. doi:10.1302/0301-
377 620X.92B1.22770.
- 378 (25) Koziara CR, Lombardo DJ, Petersen-Fitts GR, Jildeh TR, Morawa L. Effects of Cobalt and
379 Chromium Levels Following Modular Hip Stem Total Hip Arthroplasty. *Orthopedics*
380 2016;39:288–92. doi:10.3928/01477447-20160616-04.
- 381

382

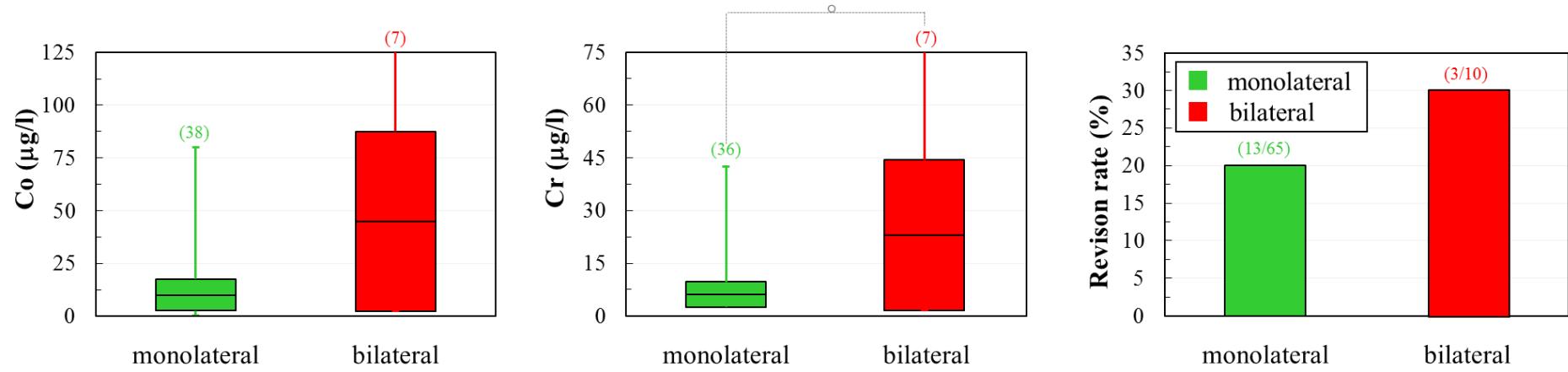


Figure 1: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) for monolateral and bilateral MoM groups.

383

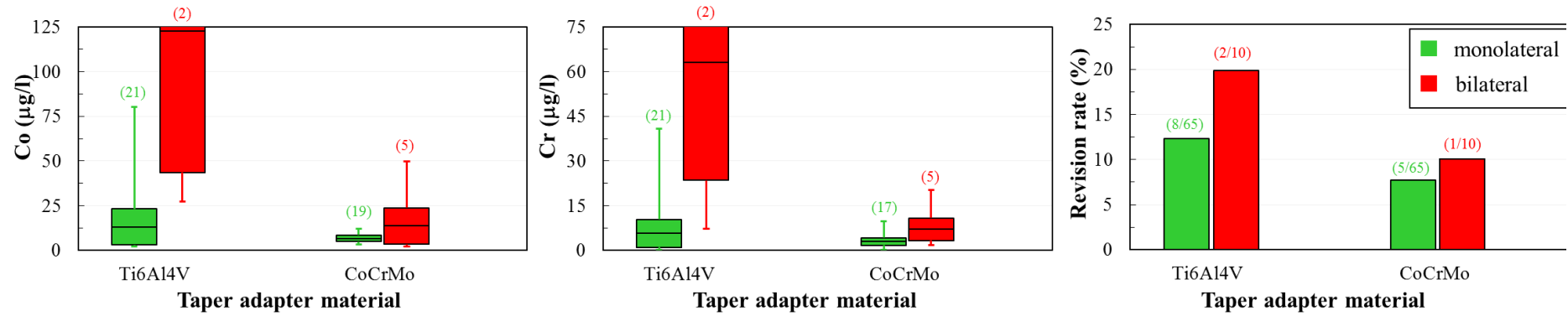


Figure 2: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of taper adapter material. Statistically significant differences are indicated (*: $p < 0.05$).

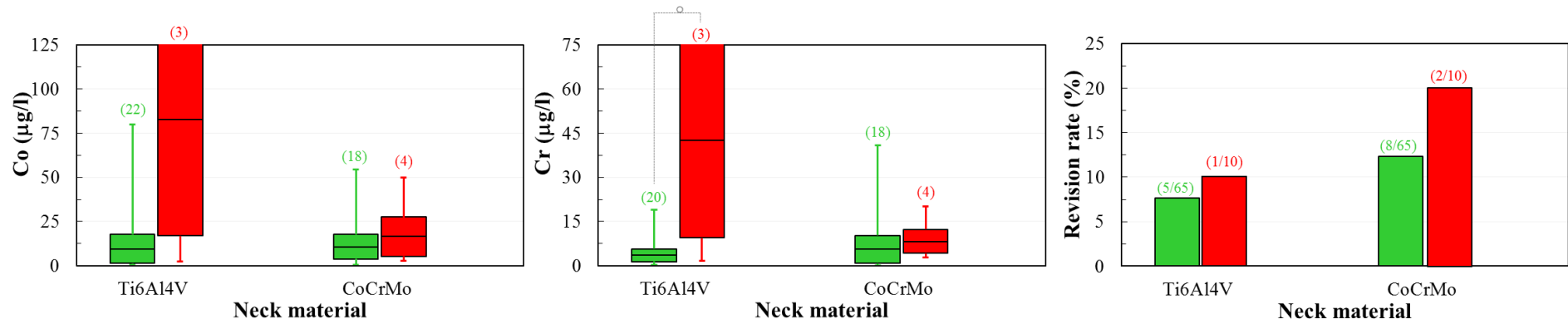


Figure 3: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of femoral neck material. Statistically significant differences are indicated (* or °: $p < 0.05$).

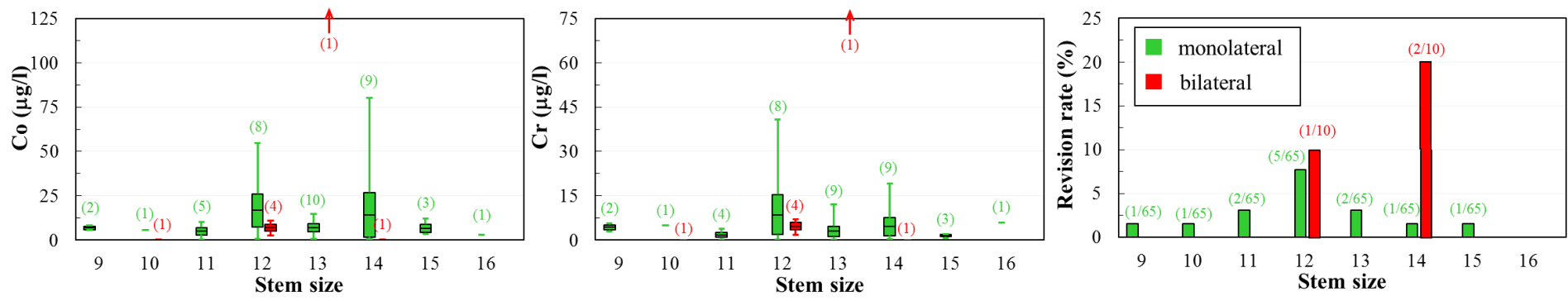


Figure 4: Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of stem size.

387

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 16.9%	0 -	11 14.7%
Patients with incomplete or not available data (#) (%)	16 24.6%	3 30.0%	19 25.3%
Number of patients with complete ions level data (male:female) (% of total population) (male : female)	38 (27:11) 58.5% (64.3 : 47.8)	7 (6:1) 70.0% (66.7 : 100)	45 (33:12) 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 (#) (% of total population)	29 44.6%	8 80.0%	37 49.3%
Positive extra-routine RX analysis (#) (% of total population)	9 13.8%	5 50.0%	14 18.7%
Patients with extra-routine MRI (conventional / MARS) analysis (#) (% of total population)	23 (7 / 16) 35.4% (10.8 / 24.6)	7 (3 / 4) 70% (30 / 40)	30 (10 / 20) 40% (13.3 / 26.7)
Patients with positive extra-routine MRI (conventional / MARS) analysis (#) (% of total population)	18 (6 / 12) 27.7% (9.2 / 18.5)	5 (2 / 3) 50% (20 / 30)	23 (8 / 15) 30.7% (10.7 / 20.0)
Number of revised patients (#) (male:female) (%) (male : female)	13 (7:6) 20.0% (16.7 : 6.1)	3 (2:1) 30.0% (22.2 : 100)	16 (9:7) 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 (Staph.Epiderm.)
M-24	n.a.	n.a.	x	-	x	Cup mobilization
M-22	o	o	o	-	x	Stem mobilization

390

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

391