REVIEW ARTICLE

Metal-on-metal bearings total hip arthroplasty: The cobalt and chromium ions release concern

C. Delaunay, I. Petit, I.D. Learmonth, P. Oger, P.A. Vendittoli

Summary With certain concerns recently reported on metal-on-metal bearing couples in total hip arthroplasty, this study’s objective is to review the current knowledge concerning release of metal ions and its potential consequences. Each metal-on-metal implant presents different tribological properties. The analytical techniques for metals are accurate and the Co ion rates seem acceptable up to 2 g/L. A delayed type IV hypersensitivity reaction (atypical lymphocytic vasculitis-associated lesion [ALVAL]) may be the source of arthroplasty failure. Idiosyncratic, it remains unpredictable even using cutaneous tests and apparently is rare (0.3%). Today, there are no scientific or epidemiologic data supporting a risk of carcinogenesis or teratogenesis related to the use of a metal-on-metal bearings couple. Solid pseudotumors nearly exclusively are observed with resurfacing procedures, carrying a high annual revision rate in women under 40 years of age, occurring particularly in cases of acetabular malposition and with use of cast molded Cr-Co alloys. Osteolysis manifests through complete and progressive radiolucent lines or through cavitory lesions stemming from ALVAL-type alterations or impingement problems or implant incompatibility. The formation of wear debris exceeding the biological tolerance is possible with implant malposition, subluxation, and jamming of the femoral head in cases of cup deformity. Moreover, each implant presents different metal ion production; assessment of their performance and safety is required before their clinical use. With the knowledge available today, metal-on-metal bearing couples are contraindicated in cases of metal allergies or end stage renal dysfunction and small size resurfacing should cautiously be used.

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KEYWORDS

- Total hip arthroplasty;
- Metal-on-metal bearings;
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- Pseudotumors;
- Resurfacing

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Introduction

Since the 1990s, osteolysis, the disease related to wear induced particle production, the diffusion of these particles within the effective joint space defined by Schmalzried et al. [1], and the cytotoxic and chemical consequences, has defined the longevity of total hip arthroplasty (THA). Second-generation metal-on-metal couple implants were introduced in clinical practice at the end of the 1980s by Weber [2], who postulated that the rate of THA loosening as a result of wear induced osteolysis would be reduced [3]. Simulators now show that standard 28- and 32-mm caliber metal-on-metal bearing systems have lower volumetric wear than equivalent polyethylene systems (PE). However, the particles generated by the metal-on-metal couples are smaller and their number is 13,500 times higher (6–7 x 10¹² to 2–5 x 10¹⁴ particles/year) than a metal-on-PE couple [4]. The metal wear debris is produced in vivo by mechanical wear, corrosion, and a combination of the two. These particles are small, from ±10 to 120 μm (mean, 40 μm), perfectly soluble, and the Co and Cr ions are bioactive.

In 1997, Brodner et al. [5] showed that the serum and blood levels of circulating metal ions rose in patients with metal-on-metal THA, particularly during the bedding-in phase, which typically lasted 2 years. In the study by Jacobs et al. [6], the circulating Co and Cr levels at 1 year were increased six and 21 times respectively, compared to the preoperative rates. Grußl presented the longest follow-up (10 years) of a series of cementless THA with a 28-mm Metasul™ metal-on-metal bearing (Zimmer, Winterthur, Switzerland) – a Co-Cr alloy with a high concentration carbon (C) – and reported a mean serum concentration of cobalt of 0.75 μg/L (range, 0.3–50 μg/L), for a threshold normal value less than 1 μg/L. The interpretation of these figures should take into consideration the complexity of taking these measurements. Each implant studied exhibited its own tribologic characteristics, often not disclosed by the manufacturer [8]. At worst, the diversity of the milieu studied (blood, serum, urine) and the sampling and analysis methods used makes any comparison between the data coming from different sources impossible.

Does the high Co-Cr rate have biological implications? Plainly, yes and already in 2003, Jacobs et al. [6] wrote: “the biological implications of elevated metal levels in the blood and urine remain the most significant concern about metal-on-metal couples” and they observed that there was little knowledge about the toxicity threshold of degradation products arising from Co-Cr alloy implants. In 2006, under the auspices of the French Hip and Knee Society (Société française de la hanche et du genou [SFHG]), a review of metal-on-metal bearing couples in hip arthroplasty validated the concept, but advised that long-term follow-up was needed to clarify the incidence of loosening and osteolysis in highly active patients [9]. Three years later, the objective of this current study, once again at the initiative of the SFHG, was to review the data available in the literature in 2009 on metal-on-metal bearings, not only with conventional arthroplasties (with femoral stems) with standard 28- and 32-mm heads — used since 1988 — but also resurfacing procedures, which were reintroduced in 1991, and more recent large-diameter bearing couple systems (2003).

Biology and cobalt and chromium ion dosing

Cobalt and chromium belong to the periodic classification of elements and are near one another in the group of metals. They are both prevalent in the environment and in food. They are indispensable to humans as trace elements in the body but are also toxic in higher concentrations. Populations studied include those who may have been exposed to the metals, in particular, foundry workers in industry. Patients with Co-Cr metal-on-metal bearings are exposed to wear with liberation of cobalt and chromium into the synovial fluid. These would migrate to the blood before being excreted in the urine.

Sampling techniques

The fluids monitored are serum, total blood, and urine. External contamination must be prevented by the appropriate choice of sampling material and method. Blood is collected at the antecubital fossa with a tourniquet using Vacutainer tubes. The main manufacturers of blood collection materials propose special trace element tubes containing an anticoagulant with a tube and cap that do not release metals. The tubes can be transported at 4°C and are stable for approximately 2 weeks with no alteration. A study conducted by Goulé on roughly 30 elements (but not chromium) showed that the cobalt concentration results revealed no significant variation if the blood was collected in Becton Dickinson classical glass tubes or special trace element tubes in polyethylene terephthalate (PET) [10]. However, any monitoring protocol should be carried out with special trace element tubes so as to standardize the collection conditions and adhere to the demands of quality assurance currently required of laboratories. For urine, a simple midstream sample collected in a urine collection cup, transported at 4°C and preserved for 1–2 weeks, is appropriate.

Cobalt and chromium analysis techniques

There are two techniques: graphite furnace atomic absorption spectrometry (AAS) and inductively coupled plasma/mass spectrometer (ICP/MS).

In AAS, the sample to be analyzed is transformed into atomic vapor in a graphite furnace heated to a high temperature (2000°C). This vapor, where atoms are found in their fundamental state, crosses a light beam whose length is specific to the element to be analyzed, i.e., 283 nm for chromium. This is chrome’s resonance line, which will allow the atom to change to the ionized state by absorbing the energy of the light that crosses the vapor, thus reducing the intensity of the line, proportional to the number of ionized atoms, at the concentration of the elements to be tested in the sample.

ICP/MS is a more powerful and high-performance technology than AAS, but at present, few laboratories have this equipment. The principle is the following: the sample to be analyzed is placed in a nebulization chamber containing a neutral gas — argon — and transformed into an aerosol of very fine droplets. The aerosol then passes through an argon plasma subjected to a very high temperature (8000–10,000°C) capable of dissociating, atomizing, and
Biochemical analysis of cobalt and chromium in urine samples can be performed by atomic absorption spectrometry (AAS) or by inductively coupled plasma mass spectrometry (ICP/MS), with high sensitivity. Cobalt's quantification threshold, around 1 \(\mu g/L\) with AAS, reaches 0.10 \(g/L\) with ICP/MS. The cobalt and chromium results are expressed either in nanomoles (international units) or more generally in micrograms/liter. Cobalt's molar mass is 58.8 \(g\) and chromium's is 51.9 \(g\). This makes it possible to deduce a conversion factor to switch from one unit to the other (Table 1).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Conversion Factor</th>
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<tbody>
<tr>
<td>Co</td>
<td>1 (\mu g) = 17 nmol</td>
</tr>
<tr>
<td></td>
<td>1 nmol = 0.06 (\mu g)</td>
</tr>
<tr>
<td>Cr</td>
<td>1 (\mu g) = 19 nmol</td>
</tr>
<tr>
<td></td>
<td>1 nmol = 0.05 (\mu g)</td>
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</tbody>
</table>

Reference values for blood and serum

Blood and serum values are evaluated in the general population, i.e., in individuals who are not exposed to these elements. For chromium, the reference values in serum are 0.50 \(g/L\) according to the National Institute for Research and Safety (Institut national de recherche et sécurité [INRS]) and are highly variable, with values from 1 to 35 \(g/L\) in whole blood reported by Lauwerys [11]. For cobalt, the usual value in serum and whole blood, respectively, is 0.4 \(g/L\) according to Lauwerys and 0.8 \(g/L\) according to the INRS [12]. Red blood cell concentrations are more a reflection of exposure over the last 3 months and the life span of red blood cells. In serum and whole blood, the reference values in exposed populations, i.e., the guidance values in France that should not be exceeded, are very poorly documented. Only the INRS provides a guide for exposure to cobalt in whole blood of 1 \(g/L\), which seems, according to Lauwerys [11], very stringent given the estimated concentration of 0.8 \(g/L\) in the general population.

The cobalt and chromium reference values in urine samples are better defined, as are many occupational medicine exposure markers. According to the INRS, the urine concentrations found in non-exposed people are less than 2 \(\mu g/g\) of creatinine for cobalt and less than 0.5 \(\mu g/g\) of creatinine for chromium [13,14]. The value of surveillance through urine sampling is to have available the limit values proposed by the INRS: 15 \(g/L\) post-shift and end of week for cobalt and 30 \(g/L\) of creatinine post-shift and end of week for chromium. However, the urine concentrations can only be used after having ruled out kidney failure.

Potential immunological effects

In patients with metal-on-metal bearing THA, high levels of circulating Co and Cr ions may be generated, and there is a positive linear correlation with a lymphocytic reactivity, along with a significant and dose-dependent reduction of the T cell CD8 marker [15,16]. On the other hand, in 2005, Willert et al. [17] described a surprising histological reaction, observed in periprosthetic tissues sampled during revisions of 19 metal-on-metal THA presenting with unexplained pain and effusion. This histological entity includes perivascular lymphocyte infiltration with accumulation of plasma cells associated with macrophages containing particles, and an increase in surface ulcerations (Fig. 1). This highly specific reaction, called atypical lymphocytic vasculitis-associated lesion (ALVAL), may initiate an as yet unknown metal-on-metal THA failure mode. Activation of T lymphocytes induces production of secreted cytokines, which results in accumulation of macrophages and an increase in phagocyte activity and lytic enzyme concentrations [18]. It is significant that, whereas 14 of these THA revised to non-metal-on-metal bearings were cured, the five who were revised with a new metal-on-metal bearing couple experienced persistent symptoms. This immunological histologic entity has also recently been reported in cemented acetabular explants that had undergone early loosening (Nich et al., unpublished data).

The frequency of hypersensitivity reactions is not well known. For Engh et al., it was 0.3% for 1379 Ultamet™ 36-mm THA (DePuy, Warsaw, IN, USA), with four revisions for ALVAL and a 7-year survival rate of 94.4% [19]. This 0.3% rate is identical to the lead author’s personal series, with one revision for femoral loosening caused by neck–cup impinge-
Metal ions and chromosome aberrations

In the in vitro studies conducted by Daley et al. [20], the wear debris artificially obtained from a simulator (caused by overload, neck–cup impingement, or microseparation) and added to fibroblast cultures for 24 hours caused aneuploidy (cell chromosome contents deviating from normal by adding or subtracting chromosomes or chromosome pairs) and translocation (exchange of segments between two chromosomes). In the in vivo study by Ladon et al. [21], with a highly sensitive detection threshold (ICP/MS at 0.2 μg/L for Co, Cr, and Mo) and analysis at specific time points over 2 years after metal-on-metal THA, the metallic wear debris caused blood lymphocyte mutagenesis in a dose-related manner. Moreover, the same team demonstrated that the aneuploidy rate observed was three times greater in the group of patients with metal-on-metal implants than in a control group of patients with no prosthesis [22]. However, there could be considerable differences between the metal wear particles obtained in vitro and in vivo. In serum, the metal particles may be covered with protein derivatives, identified as self and, therefore, not phagocytosed by macrophages. Furthermore, identical and equally numerous chromosome aberrations were detected in the whole blood of patients with ceramic-on-ceramic couple implants, which points toward an as yet unknown mechanism causing these manifestations [23]. Be that as it may, the long-term clinical implications of these anomalies remain poorly characterized today, and enlightenment can only come through epidemiological data provided by arthroplasty registries [24].

Teratogenic and carcinogenic risks

Metal ions can cross the placental barrier, but critical levels vary depending on the bearing system studied and the sensitivity of the analysis technique used. With a 28-mm Metasul bearing with a high carbon concentration on a conventional hip prosthesis (Alloclassic-CSF, Zimmer), placental passage measured by AAS was low [25] but was more significant analyzed by ICP/MS with a Birmingham Hip Replacement (BHR) [26]. Nevertheless, the placental barrier seems partially effective, since the ion rates found in cord blood in both studies were nil or less than the rate found in the mother. There have been no reports of teratogenicity in the literature to date, and current knowledge is based on speculation. In 2007, the Medicine and Health Regulatory Agency (the British equivalent of the French AFSSAPS) concluded that there was no proof of any clinical expression of genotoxicity induced by high levels of metal ions [24]. Nevertheless, prospective studies are under way in Great Britain, comparing the presence and progression of chromosome changes in peripheral blood lymphocytes in young women of childbearing age who have a variety of resurfacing prostheses.

Visuri et al. [27,28] have found no epidemiological evidence of any carcinogenic risk caused by metal ions in the Scandinavian registries. The persistence of a slight increase in hemotological neoplasia is offset by a slightly reduced incidence of other cancers.

Local toxicity of cobalt and chromium ions

The increase in the blood levels of metal ions, the description of delayed hypersensitivity reactions, as well as the demonstration of pseudotumors have become almost obsessional topics. Has the concept of metal-on-metal bearings generated more fearsome complications than those encountered with other bearings?

Pseudotumors

In 2006, Boardman et al. [29] published a case of a solid tumor related to a resurfacing procedure. In 2008, Pandit et al. [30] reported 20 cases of pseudotumors in different types of resurfacing (BHR, Conserve Plus, Cormet) but only with female patients. These tumor lesions were not specific to metal-on-metal couples since several publications exist of cystic-type tumors occurring with metal-on-polyethylene bearings [31—35]. The clinical examination can identify a palpable mass on the anterior or lateral surface of the hip or even in the iliac fossa. Local erythema is possible and infection is occasionally suspected [36]. Pain can vary from simple discomfort, a sensation of local tension, or it can be significant, leading to major functional handicap. Instability (subluxation, dislocation) has also been described, particularly in cases of substantial joint effusion [37].

Pseudotumors can also be responsible for vascular compression syndromes with edema of the lower limb. Butler and Barrack [38] reported two cases of iliac vessel compression due to a pelvic cystic mass occurring as a result of polyethylene wear of the insert. Paralysis of the femoral nerve or lateral cutaneous nerve involvement in the thigh have also been described [39], Clayton et al. [40] reporting one case after resurfacing and Pandit et al. [30] three other cases.

The imaging workup should include plain X-rays of the pelvis and hip, with measurement of cup inclination. Ultrasound identifies whether the mass is solid or fluid. The CT scan defines implant position, particularly anteroposterior (version), and demonstrates the tumor location and its extension. MRI analyzes the tumor characteristics: cystic, solid, or mixed.

Cystic lesions

Thirty-seven cases have been described, 34 of which for metal-on-PE implants [31—35,37]. They can stem from abnormal wear, loosening, or infection [31,36—38,41]. Wear debris (PE or metal) leads to an inflammatory reaction with an increase in the volume of joint fluid. The fluid under pressure can escape through the iliopsoas bursa if this communicates with the joint or through a breach created by the surgical approach [42].

Solid or mixed lesions

Today, these lesions are for the most part associated with resurfacing [30]. Twenty-four such cases have been described [29,30,40,43]. Symptoms appear early, at a mean 17 months (range, 0—60 months). They are located prefer-
Conventional metal-on-metal implants and osteolysis

Osteolysis related to metal-on-metal bearing implants is rarely mentioned in the literature and, when it is, the evaluation criteria according to Zicat et al. [50,51] are not always specified. The clinical and radiographic characteristics differ from those of osteolysis from polyethylene resorption granulomas in the sense that functional and radiological signs appear earlier [52–55].

How these lesions evolve varies depending on the etiology (metallosis from impingement, delayed hypersensitivity), the type of acetabular implant fixation, and the type of alloy (high or low carbon content, even the combination of the two). Osteolysis involves mainly the femoral side at Gruen et al.’s zones I and VII [56] and exhibits a cavitory appearance [52,54]. Acetabular osteolysis can also be cavitory in De Lee and Charnley’s zone I [57]. Radiolucent lines mainly involve the cup, reaching zones I, II, and III. At the femur, the radiolucent lines are found in Gruen zones I, VI, VII, and VIII.

Cemented acetabular fixation directly into the bone (without using cage reinforcement) with a metal bearing insert has proved its non-reliability. Lazennec et al. [53] found 31% radiolucent lines, 11% progressive, Nich et al. [55] 27% progressive, and Levai et al. [58] 15%. Lazennec et al. [53] described a 5% acetabular and 8% femoral rate of osteolysis. Long et al. [59] found only non evolving radiolucent lines but at a high rate of 20%. However, the results of this type of implant reported by Girard et al. [60] proved to be satisfactory at the medium term when they were cemented in metallic supports (reinforcement cages).

The cementless implants with a Metasul™ insert have demonstrated greater reliability. The osteolysis rate was 0–1% for Delaunay et al. [61,62] and 3% for Beldame et al. [52] (Fig. 3). Eswaramoorthy et al. [63] noted 5% non-progressive acetabular radiolucent lines at 10 years [62]. Sharma et al. [64] observed 18% stable acetabular radiolucent lines and femoral radiolucent lines in 17% of cases with a mean of more than 7 years of follow-up. Long et al. [59] noted 6% calcar resorption under the cementless femoral stem collar and Migaud et al. [65] 80% calcar atrophy with no osteolysis of cementless implants at more than 5 years of follow-up. Goetz et al. [66] believes this calcar resorption does not correspond to osteolysis. However, with a longer mean follow-up of 92 months, Holloway et al. [67] reported five cases of acetabular osteolysis with 22 cementless Metasul Fitek™ cups (Zimmer, Winterthur, Switzerland), with an excellent clinical result in active patients with a mean age of 49 years. The histological study in the only implant revised for osteolysis could not implicate the involvement of metal debris, since no debris was found in the tissues examined. The same was true in Carr and DeSteiger’s series [68], who, with the same implants, reported three revisions of Metasul 28-mm bearings for proximal femoral osteolysis, a 2.6% prevalence after 3–9 years follow-up, with no loosening, impingement, or metallosis at revision.

Other chromium-cobalt-molybdenum alloys have been used in bearing systems. These alloys differ in their carbon contents (high grade greater than 0.2% and low grade less than 0.07%). They also differ in how they are manufactured
Metal ions and metal-on-metal bearings in total hip arthroplasty

Figure 3 Proximal osteolysis in zone 7, 5 years after implantation of a hip prosthesis with hybrid fixation.

(cast or wrought metal). With an Ultima™ insert with a high-grade carbon and a low-grade S-ROM head, Park et al. [69] described an early 5.9% osteolysis rate (24 at 41 months): the osteolysis was centered in the greater trochanter. With the Sikomet™ bearing (ex-EndoPlus, Smith and Nephew, Courbevoie, France) with a low carbon content, Milosev et al. [54] found a 2.5% osteolysis rate with a mean follow-up of 7 years; this was linear or extensive in zones I and VII of the femur and zone I of the acetabulum. With the same Sikomet™ implants, Korovessis et al. [70] observed 5% femoral osteolysis, with 5—9 years of follow-up. With a high carbon content Lubrimet™ implant, at more than 10 years of follow-up, Neumann et al. [71] observed 4% femoral osteolysis in zones I and VII, and 2% in zones II, VI, and VIII.

Since volumetric wear decreases with the increase in carbon content, it seems preferable to use implants with a high-grade metal-on-metal bearing couple. The size and shape of the particles are not modified by the carbon content and, therefore, do not explain the different reactions associated with different metal-on-metal implant.

Osteolysis and resurfacing

The goal of resurfacing is optimal preservation of femoral bone. In this type of implant, it is impossible to precisely analyze the extent of femoral osteolysis. Only a progressive decrease in the neck diameter can be evaluated. This reduction was found in 2.8% of Conserve+ cases by Amstutz and le Duff [72] and in 14.5% by Heilpern et al. [73] with BHR resurfacing. On the acetabular side, with the same BHR implant, Treacy et al. [74] did not mention osteolysis, whereas Steffen et al. [75] reported an 8.2% rate of acetabular radiolucent lines.

Resurfacing and large-diameter metal-on-metal THA

The level of metal ions in the postoperative period is an indicator of the performance of the bearing surfaces and also allows ongoing surveillance of the implant, even if acceptable levels of Co and Cr ions have not yet been agreed by the orthopaedic community. Be that as it may, the levels of metal ions in 28-mm Metasul™ bearings (Zimmer), in use for more than 20 years, gave similar results to the historical McKee-Farrar prosthesis [7]. These Co ion levels (approximately 1 ug/L) should be considered the standard in metal-on-metal hip replacement, and new developments should aim to reproduce them or reduce them further. The material and design features of the implant that influence metal-on-metal joint surface wear include: the diameter of the bearing couple, the quality of the surface bearing, the sphericity of the component, joint clearance, the manufacturing process (forged metal versus cast metal), and carbon content. The tribologic data show that, with equal clearance, a large-diameter component will create a thicker liquid film between the convexity of the femoral head and the concavity of the acetabular component, thus minimizing wear [76—78]. However, most of the data published on the metal ion levels with large metal-on-metal bearings have shown levels of Cr and Co ions at best similar to or higher than those with 28-mm Metasul™ bearings [79,80].

Wear of joint surfaces is not the only source of metal ion release. It has been demonstrated that conical modular junctions also release a significant amount of metal ions through corrosion. This phenomenon is produced for all THA modular implants and its magnitude can be related to the number and quality of the metal junctions [81]. In addition, the metal surface of the implants can be the site of passive corrosion in contact with organic fluids, also generating ion release. This corrosion is produced when the protective film is damaged or interrupted by friction or micromovement, leading to contact between the body fluids and the metal implants.

Over the past few years, we have measured the concentrations of Cr, Co, and titanium (Ti) in patients with a Metasul™ 28-mm prosthesis, hip resurfacing (HR), and in four types of large-head diameter, metal-on-metal THA (Fig. 4). Comparison of these different groups has made it possible to draw certain conclusions on the effects of different characteristics of bearings and various implants.

28-mm implants and resurfacing

In a randomized controlled trial comparing Durom™ (Zimmer) hip resurfacing and 28-mm Metasul™ CLS/Allofit™ THA (Zimmer), we measured significantly higher levels of Cr and Co at 3 months in the hip resurfacing group compared to the 28-mm THA group (2.0 versus 1.5 μg/L, p=0.036 for Cr, and 0.9 versus 0.7 μg/L, p=0.035 for Co) [82]. How-
ever, at 24 months postoperatively, no significant difference persisted (1.6 versus 1.6 μg/L, \( p = 0.819 \) for Cr, and 0.7 versus 0.9 μg/L, \( p = 0.207 \) for Co, for hip resurfacing and THA, respectively). In the HR group, the concentration stabilized at 1 year, after the bedding-in period, in comparison to the 28-mm THA group, in which the metal levels stabilized at the end of the 3rd month. This study is reassuring because it demonstrates that this large-diameter joint surface can produce, in vivo, Cr and Co ion rates comparable to the 28-mm Metasul™ standard. However, these results do not provide any conclusion about the effect of the couple diameter on ion production. Even though both groups in our study had forged alloy implants (high-grade carbon Cr-Co-Mo with the same surface roughness and the same sphericity), they did not have identical joint clearance (≈ 45 μm for the 28-mm THA versus ≈ 75 μm for the HR). The only means of determining whether couple size influences the level of metal ions and wear would, therefore, be to evaluate a sufficiently large cohort of hip resurfacing patients with fixed joint clearance, whatever the implant diameter.

It is noteworthy that for both groups (HR and 28-mm THA), we observed higher mean concentrations of ions (Cr, Co, and Ti) in patients with acetabular components smaller than 54 mm and in women. Given that the diameter of the bearing is fixed in 28-mm THA, the larger bearing diameter in HR cannot be considered a favorable factor for reducing ions with the larger components. Similarly, the present study showed a high level of Ti ions in 28-mm THAs and in HR (1.3 versus 1.9 μg/L at 24 months, \( p = 0.001 \)). Since Ti is not present on the bearing surfaces, its release results from passive corrosion of the metal. A negative correlation was noted between the component size and the Ti level. Since large-diameter implants have a potentially greater susceptibility to corrosion, a positive correlation could have been expected. Sex may, therefore, be the main factor affecting the metal ion levels (women have higher ion levels). The difference in ion levels between males and females may be secondary to a variant in the metabolism of metal ions (different lean mass, cellular or extracellular storage, or renal excretion). More in-depth research is undoubtedly necessary to better understand the metabolism of metal ions. Different pelvic morphology and gait may also contribute to elevated ion levels in the female.

**Resurfacing and large-diameter THA**

To quantify the portion of Cr and Co ions released by corrosion at the conical junction on the femoral neck and the passive corrosion from the metal implant surface, we compared the results of Durom™ (Zimmer) LDH-THA to those using the Durom™ HR system, which both have identical bearing characteristics [83]. There was no difference between the two groups in terms of the patients or the implant sizes (\( p = 0.092 \) and 0.912). We detected mean Co concentrations that were 3.3 times higher in LDH-THA than in HR (2.2 and 0.7 μg/L, \( p < 0.001 \)).

Marked differences between HR and LDH-THA can be attributed to two main factors. The first factor is that the tested LDH-THA system incorporates an open femoral head model with head sizes 50 mm and larger. The open femoral head model is associated with a 67% increase in ion release (3.0 μg/L for open heads versus 1.8 μg/L for closed heads; \( p = 0.037 \)). A possible explanation is that the open femoral head model provides a larger surface contact for passive corrosion of the metal. This factor seems more important than the theoretically favorable tribologic effect of the larger diameter and the effect of sex (women were associated with a smaller bearing diameter and higher levels of metal ions).

The second factor, possibly responsible for the significant differences observed, relates to the fact that the LDH-THA system used incorporates a Cr-Co sleeve adaptor for adjusting the neck length (dual conical junction). To determine the influence of adding this modularity, and to eliminate the bias...
introduced by the femoral head model (open versus closed), we compared the femoral components with a diameter less than 50 mm in LDH-THA (closed femoral head models) and HR. At 1 year of follow-up, the mean concentration of Co was significantly increased, by 157% for LDH-THA less than 50 mm compared to HR less than 50 mm (1.8 versus 0.7 μg/L, p < 0.001). The main hypothesis to explain this difference is the release of ions at the Cr-Co metal modular junctions related to the addition of this sleeve adaptor.

Adding a dual conical adaptor as well as an open femoral head model to LDH-THA was, therefore, a greater source of metal ion release than joint surface wear. Industry, therefore, forfeited all the tribological advantage of a large head in an attempt to reduce inventory. Furthermore, in the LDH-THA, no significant variation between 6-month and 1-year follow-ups was noted in the metal ion concentrations, whereas with the HR, Co decreased significantly between 6 months and 1 year (t-test for matched samples, p = 0.0114). This suggests that even after having reached steady state wear, the LDH-THA system continues to release a large quantity of metal ions resulting from wear and passive corrosion at the conical junctions. Additional follow-up is, therefore, needed to determine whether the maximum levels are reached. These results raise considerable concerns regarding the effects of adding modularity on metal ion release and requires further research on LDH-THA.

**Comparison of four types of large-diameter THA**

We compared 112 patients who had received one of the four different brands of LDH-THA: Magnum/Recap™ (Biomet, Warsaw, IN, USA), ASRTM (Depuy, Warsaw, IN, USA), Bingham Hip Replacement™ (Smith & Nephew, Memphis, TN, USA), and LDH Durom™ (Zimmer) with a prospective study of the metal ion levels [84]. At 12 months after implantation, the Co ion levels were similar except for the Durom™ LDH, which exhibited a higher Co level. All the results were higher than the concentrations of Co ions found at 12 months in the Durom™ HR (0.7 μg/L). Yet, all the LDH implants present a Cr-Co conical modular adaptor for length adjustment, except for the Magnum/Recap™ system whose adaptor is made in Ti.

**Interpretation of comparative studies**

Other than bearing couple surface wear, passive corrosion of the exposed metal surface is a factor influencing the metal ion concentrations in the synovial fluid and blood. When interpreting and comparing the different implants, it is difficult to establish exactly which proportion of the Cr and Co metal ions come from passive corrosion of the joint surfaces, the fixation surface, the cone-shaped junction (in the THA), and finally wear of the bearing couple surface. To estimate the effect of passive corrosion in our studies, we decided to measure Ti (a metal that is not part of the joint surfaces) in our patients. We observed significantly high levels of Ti in all the study groups. Jacobs et al. [81] obtained very similar results at 3 years after implantation, with a tripling of Ti ions (4.13 μg/L) in a THA group with the Harris-Galante II™ cup covered with porous Ti. In their 30-year follow-up of patients with a Ti THA, Dunstan et al. [85] reported a 50% increase in Ti ion concentration.

In addition, corrosion and wear between two different metals at the conical junctions is a known source of high metal ions in the body. The phenomenon is present in all modular hip implants, and its magnitude may be related to the number and quality of these metal junctions. High concentrations of Ti ions could thus be directly proportional to the metal surface exposed to passive corrosion. This is very difficult to estimate, however, with plasma spray coating. However, the porous character of the treated zone significantly increases the surface exposed to Ti corrosion when compared to coatings whose surface was treated simply with sandblasting.

Taking into account the effects of metal corrosion on the ion level, it is probable that the differences between the various LDH-THA and HR systems results in part from metal ion sources other than those related to joint surface wear itself, particularly when comparing components using different fixation methods (i.e., cemented or cementless femoral components) and different surfaces for cementless fixation (i.e., Cr-Co or plasma spray coating with Ti). For example, Cr and Co ion production from Durom™ HR is clearly less than the ion data published from other brands such as the BHR (Smith & Nephew) and the Cormet 2000™ [83,84]. These other RH systems present a porous surface of the acetabular component in Cr-Co for secondary fixation (which can be a considerable source of Cr-Co ions through passive corrosion) compared to the Durom™ system (which uses Ti plasma spray coating for fixation). However, it is difficult to determine which situation is the best: a higher level of Cr-Co while avoiding Ti or a lower level of Cr-Co and Ti release. Very little research has been done on the biological effects of high Ti levels on the human body. The advantages of Ti include a low elasticity modulus, very little immunogenicity, and a high affinity for fixation through bone ingrowth on the implant. Chronic occupational exposure to titanium tetrachloride can lead to its selective accumulation in the lungs and adjacent lymph nodes and may be the cause of pulmonary granulomatosis [86]. In his study comparing tissue reactions to particles of Cr-Co, Ti, and polyethylene in the failure of total knee arthroplasty (TKA), La Budde et al. [87] observed that Ti was associated with a severe giant cell reaction, whereas Cr-Co presented significantly more histiocytes per field (101.5 versus 40.4; p = 0.002). They concluded that “this study demonstrates no difference in acute or chronic inflammatory reaction between the two alloys”. Ti acetabular and femoral implants have been used very successfully in THA for decades. As shown by our earlier study, the CLS/Allofit THA releases a large quantity of Ti, even 2 years after implantation (1.30 μg/L at 2 years versus 0.57 μg/L preoperatively). Yet, this type of femoral stem and other similar stems have been implanted in large numbers throughout the world over the past 25 years. The level of Ti in our HR cases at 2 years was 1.87 μg/L, corresponding to 1.4 times the level with cementless THA.

Moreover, even though the ion levels reported with Durom™ LDH-THA are higher than those with HR and other LDH systems tested, they remain comparable to the concentrations measured after TKA (Cr, 0.92 μg/L; Co, 3.28 μg/L), after spinal column surgery (Cr, 1.0–10.5 μg/L and Ti, 2.6 μg/L), or after intramedullary nailing of the tibia
It is surprising to observe that little mention was made of the potentially adverse effects of metal ions in orthopaedic domains other than hip arthroplasty, where, for example, young women who have undergone vertebral arthrodesis to correct scoliosis continue to carry their metallic instrumentation during pregnancy and breastfeeding.

Conclusions

Using appropriate methodology for trace element analysis, assessment of cobalt and chromium is sensitive, accurate and reproducible. The rate of circulating Co and Cr ions is low when the bearing couple functions well (Co < 1 μg/L).

Hypersensitivity is idiosyncratic, unpredictable with cutaneous tests, specific to metal-on-metal couples, and apparently rare: 0.3%.

Metal-on-metal bearing couple surfaces allow the surgeon to increase the size of the femoral head in THA. This is advantageous from a number of points of view, in particular for joint stability and to prevent component impingement. However, this new technology has been associated with new problems. In addition to joint surface wear, passive corrosion of metallic surfaces exposed to biological fluids is a factor influencing ion concentrations. When evaluating metal ion release arising from metal-on-metal THA, one should consider the total load of metal coming not only from bearing wear but also from metallic junctions wear and implant corrosion. Each implant using metal-on-metal bearings has its own characteristics; assessment of their performance and safety is required before they are widely used.

Metal-on-metal implants do not tolerate any malposition. Similarly, female sex seems to be significantly associated with higher circulating metal ions, undoubtedly related to the use of smaller components. Patients with a long life expectancy with high ion values have a greater long-term risk of undesirable side effects than those with normal levels. Identification of the factors that adversely affect the bearing should remain a research priority and requires collaboration between clinicians, epidemiologists, and industry.

Conflicts of interest statement

Dr C. Delaunay is consultant for Zimmer, Dr I. Learmonth is consultant for Depuy, Dr P.A. Vendittoli is consultant for Zimmer, Stryker and Wright medical.

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