Metal-on-metal hip prostheses: Correlation between debris in the synovial fluid and levels of cobalt and chromium ions in the bloodstream

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Received: 26 July 2013 / Accepted: 19 September 2013 / Published online: 12 October 2013
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Abstract

Purpose Hip prostheses with metal-on-metal (MoM) coupling can release cobalt-chromium particles and ions. The aim of this work is to verify the correlation between particles in the synovial fluid and circulating ions.

Methods Forty patients were enrolled; particles from synovial fluid were analysed by SEM–EDX (Scanning Electron Microscopy–Energy Dispersion X-rays analysis) and levels of circulating Co and Cr were assayed by ICP–MS (inductively-coupled plasma mass spectrometry).

Results In 16 cases we did not find any particles in the synovial fluid and the Co level in whole blood was 0.05–4.42 ppb; in seven with few particles the blood level was 2.2–15.6 ppb; in six cases with several particles the level was 5.0–54.3 ppb; finally, in 11 cases we isolated not only Co–Cr particles, but also

Cr particles with low or absent Co and in these patients the circulating level of Co was 23.8–109.6 ppb. Co in serum and Cr level both whole blood and serum have shown a similar trend to Co; the correlation between all these values and the corresponding particles is statistically significant in all cases.

Conclusion Co and Cr both in serum and whole blood represents a systemic representation of the particle release at local level and can therefore be used to confirm a diagnosis and monitor the wear process of MoM articular prostheses.

Keywords Hip prosthesis · Metal-on-metal · Cobalt · Wear · Corrosion

Introduction

First-generation metal-on-metal (MoM) total hip prostheses (Mc Kee–Ferrar and Ring) were introduced at the early stage of hip prosthesis development but were abandoned during the 1970s in favour of metal-on-plastic (MoP) devices that were cheaper and more promising [1]. Second-generation MoM THR devices (1980s to present) were introduced with the intent to address issues of osteolysis and aseptic loosening found with MoP devices [2].

To date, approximately 1 million MoM hip prostheses have been implanted worldwide. These implants have articular components typically composed of cobalt–chromium–molybdenum alloys. Despite the minor volumetric wear compared to MoP, and a probable reduced risk of osteolysis and consequent aseptic loosening, hip MoM prostheses did not reach the level of survival expected, as demonstrated by the major registers [3–6].

This is probably linked to the damage of the articular surfaces being such as to cause the release of significant amounts of Co and Cr. The situation is negatively affected by the use of large heads (≥ 36 mm of diameter) where the

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presence of a fan adapter (sleeve) often induces corrosion phenomena at the taper-trunnion interface, with further release of products in the periprosthetic spaces.

The wear and corrosion debris from MoM hip replacements could be the cause of a local soft-tissue inflammatory response, leading to the premature failure of the implant [7–9].

Cr and Co are essential microelements required for normal biological functions, but at high concentrations they are toxic and are known to interfere with a number of biological processes [10–13]. Monitoring of patients with MoM prostheses with heads around 36 mm is currently under great debate. There are different indications in the United States, where the FDA has stated that there are not scientific data supporting the dosage of ion levels as a prognostic factor for the hip functionality, or for the possible wear of the implant or for the development of local and/or systemic toxicity reactions; this is also true in Europe, where the value of blood Co of 7 ppb has been identified by Medicines and Healthcare products Regulatory Agency as the threshold for closer follow-up [14], although not all authors agree on this level and some suggest a lower security level of 4 ppb [15].

Recently, many reports have shown several cases of patients with MoM hip prostheses where a remarkable increase of Co and Cr concentrations in blood and joint synovial fluid has been reported [15, 16].

Fluid from the hip joint is the first biological fluid into which the debris are released, but such samples are more difficult to retrieve compared to venous blood, and their diagnostic value must therefore be carefully considered [16]. For this reason many authors have verified the existence of the correlation between blood and synovial fluid levels of these ions [8, 17, 18].

What still remains to be verified is the correlation between wear/corrosion particles isolated in the synovial fluid and the blood level of Co and Cr that are responsible for the systemic toxicity attributed to MoM prosthesis.

Therefore, the aim of this study was to verify whether the measurement of blood/serum metal-ions can mirror the damage of the prosthesis at joint level.

Methods

Patients

After approval by the institutional review board and signature of informed consent from each patient, 40 patients were selected for this retrospective and analytic-observational study amongst those admitted to the Rizzoli Orthopaedic Institute of Bologna for assessing their clinical situation or revising unilateral MoM stemmed THA. All patients suffered from pain due to mobilisation of one component or to local implant reactions, often associated with metallosis. We excluded patients where sepsis was ascertained or suspected and who had other metal

devices implanted that could affect blood levels of metal ions. For all 40 patients the synovial fluid and blood samples were collected on the same date or in consecutive days. Six patients had metal head with diameter less than 36 mm, and 34 had a metal head with diameter around 36 mm. Of these, almost half had an ASR Depuy head and acetabulum and the other half had different manufacturers such as Smith and Nephew, Zimmer, Biomet. ASR Depuy THA are evidenced due to specific voluntary recall which occurred in September 2010. Twenty four patients were females, mean age was 61 years and mean follow-up was 4.4 years.

Detection of particles in synovial fluid

Synovial fluid samples were obtained either intra-operatively, after the joint was exposed during revision surgery (carefully avoiding dilution with blood from the surgical dissection), or by using an ultrasound-guided hip needle aspiration according to a published guideline [19] and then stored at -80°C until the analysis was performed.

Briefly, 200 microliters of synovial fluid were placed directly onto the glossy side of a polycarbonate filter (0.2- μm pore size) then digested by at least three subsequent additions of sodium hypochlorite (Sigma Aldrichs, St Luis, MO, USA). Filters were then mounted on SEM holders by bi-adhesive tape, gold sputtered and examined with a Cambridge Stereoscan 200 electron microscope operated at 20 KV. Micrographs were taken at 10,000X magnification. Quantification was defined by 20 fields capturing 90 μm^2 each, representing all the regions of the filter. The particles were counted, their major diameter measured and their chemical composition was verified by energy dispersive X-ray microanalysis; analysis was performed at 25-mm WD with an Oxford INCA Energy 200 apparatus [20]. The amount and the chemical composition of metal particles were then scored for each sample by two separate operators.

All results were matching and they were classified in four levels (absent, physiological, mild and strong) based on the number and chemical composition of the Cr-Co particles (Table 1).

This score was set on the basis of our previous experience on ceramic particle presence in synovial fluid [21] and peri-implant

Table 1 Score adopted for quantification of metal particles isolated in synovial fluid in metal-on-metal (MoM) hip

Score	Number of Co-Cr particles observed in 20 fields	Presence of Cr particles with low/null content of Co
0 : absent	0 Co-Cr particles	None
1 : physiological	1–5 Co-Cr particles	None
2 : mild	More than 5 Co-Cr particles	None
3 : strong	More than 5 Co-Cr particles	At least 1

tissues [22]. Conversely to the effect of ceramic particles, where no changes in the chemical composition are observed compared to the implanted component, with MoM devices particles can be found where the Co/Cr ratio of the initial alloy is not maintained. Such particles indicate a chemical attack (corrosion) that affected the surfaces and in particular the trunnion–taper interface [23]. Preliminary assays (data not shown) have ascertained that chemical digestion of particles, does not alter their composition, at least at EDX sensibility.

Cobalt and chromium assay in blood

Blood samples were obtained using a disposable intravenous cannula; the first three millilitres were discarded and a further five millilitres of blood were withdrawn and transferred into a separate trace element BD vacutainer tube (Franklin Lakes, NJ, USA) containing sodium ethylenediaminetetracetic acid (EDTA) to collect whole blood, while a further five millilitres were transferred into a trace element serum BD vacutainer tube, and then centrifuged at 800 rcf for seven minutes for serum collection. The samples were frozen and stored at -20°C until the analysis was performed.

ICP-MS (ELAN DRC II, Perkin Elmer, Waltham, USA) equipped with dynamic cell reaction (DRC) was used for whole blood and serum samples. A reaction system with ammonia gas was used for the elimination of spectral interferences. The samples of serum and blood were diluted (1:20) with Triton 0.05 % for inorganic trace analysis (Merck KGaA). The curve and sample solutions were pumped in the spray chamber using a peristaltic pump. The blank samples were used to correct for any contamination in each batch. The concentration of metal ions was expressed as ppb. The calibration standards were prepared by standard solutions of single elements ranging from 0.5 to 1,000 ppb: cobalt in HNO_3 2 % mono elemental standard solution (Carlo Erba Reagenti, Milano, Italy) and chromium in HCl atomic absorption standard solution (Sigma-Aldrich, Milwaukee, USA). The accuracy of the method was determined according to the mean values obtained on certified reference materials (Environmental and Occupational G-EQUAS for blood and serum, Erlangen, Germany).

The coefficient of variation was 6.1 % and the limits of detection, calculated as three standard deviations of the background signal obtained on ten white samples, were 0.05 ppb in all the matrices. The method accuracy was assessed by the external quality assessment program and it was certified for the above-mentioned metallic elements by G-EQUAS of the German Society of Occupational and Environmental Medicine.

Statistical analysis

The correlation analysis between metal ion measures in whole blood and serum samples and the presence of chromium and

cobalt wear particles detected in the synovial fluid samples were analysed using Pearson's correlation coefficient (r) and the statistical significance of the correlation (p).

Statistical analysis and graphs were performed using SPSS v. 14.0 software (SPSS Inc., IBM, Chicago, IL, USA).

Results

Synovial fluid particles score resulted 'absent' in 16 cases, 'physiological' in seven, 'mild' in six cases and 'strong' in the remaining 11 patients. Particles observed in patients with 'physiological' and 'mild' scores were mainly egg-shaped with the longest diameter shorter than 1 micron. In 'strong' score patients, the particles where the Co/Cr ratio was conserved had often bigger sizes, up to 5 micron; particles with an altered Co/Cr ratio had irregular shape and size between one and five microns. In Fig. 1 the results of the particles score are presented according to diameter of the prosthetic head.

Co and Cr values in whole blood and serum measured in the 40 patients are summarised in Table 2.

The results obtained in the synovial fluid samples were then correlated with Co and Cr ion values in the corresponding whole blood and serum samples measured.

A strong positive correlation between Co and Cr particles detected in synovial fluid and the metal ions measured both in the whole blood and in the serum samples was found (Table 3). The highest correlation was found between particles and cobalt.

In Fig. 2 the relationship between circulating ions and scored particles in synovial fluid is shown.

Discussion

This study aimed at verifying whether the Co and Cr particles isolated from synovial fluid of patients implanted with MoM hip prostheses are related to the Co and Cr ions measured in

Fig. 1 Debris score observed in the 40 patients, grouped according to their head diameter. Large heads are split between ASR and 'all the others'

Table 2 Median and range of cobalt and chromium levels in whole blood and serum of metal-on-metal (MoM) patients

Measure	Small head (<i>n</i> =6)		Large head, no ASR (<i>n</i> =17)		Large head, ASR-Depuy (<i>n</i> =17)		Total (<i>n</i> =40)	
	Median	Range	Median	Range	Median	Range	Median	Range
Cobalt in whole blood	1.4	0.5–104.4	2.5	0.3–101	22.8	0.05–109.6	6.2	0.05–109.6
Cobalt in serum	1.5	0.6–87.8	2.6	0.5–112.3	18.5	0.8–131	7.3	0.5131
Chromium in whole blood	1.4	0.8–54	2.3	0.1–60	7.4	0.5–99.3	3.59	0.1–99.3
Chromium in serum	1.8	1.1–55.4	2.0	0.3–99.2	9.5	0.8–98.8	4.5	0.3–99.2

their whole blood and serum. The synovial fluid is indeed the first biological fluid where the wear debris from articular surfaces, and eventually corrosion products originating from the taper-trunnion interface, are released, and the proof that the measurement of blood/serum metal-ion mirrors the situation at articular level is essential.

In the record of cases analysed, a statistically significant correlation has been found between concentration and type of debris of the Co-Cr alloy present in the synovial fluid and the circulating ion levels. The correlation is statistically significant both for Co and Cr but is slightly higher for the ion cobalt. In the absence of particles in the synovial fluid, the circulating values of Cr or Co are lower than 7 ppb in 15 cases out of 16 and establishing values slightly higher than that proposed by Estey et al. [15], suggesting 4 ppb as normal threshold level of ions for asymptomatic subjects. With the increase of the number of Co-Cr particles isolated in the synovial fluid, the level of circulating ions increases. The maximum level has been observed in synovial fluid particles that do not maintain the initial alloy Co/Cr ratio, but show instead a low percentage or absence of cobalt. It should be noted that in these cases (11 out of 40 of our patients), despite the selective loss of cobalt

from the degradation products of the prosthesis, the Co/Cr ratio is not different from that observed in all other cases; therefore, the ratio between the two ions is not a predictive element of the prosthesis condition, while its absolute values are. Moreover, it has been confirmed that the level of particles released locally, and the consequent blood level of Cr and Co, is higher in the ASR prosthesis compared to the other MoM with the same head dimension range, even if cup positioning has not been taken into account.

To our knowledge, there is no evidence in literature correlating the quantity and quality of debris coming from the MoM prostheses, and isolated in the synovial fluid, with the circulating levels of Co and Cr; a methodological and precise method was set up by Billi, but it was applied to two samples obtained in a wear simulator in bovine serum [24].

Some authors have analysed the debris isolating it from the tissues. For example, Doorn et al. analysed the particles isolated from periprosthetic tissues, coming from MoM prostheses of the first generation, which therefore cannot be comparable with the current status [25]. More recent studies have reported that the majority of particles were Co-Cr, while some contained no cobalt [26].

Table 3 Levels of Co and Cr circulating ions according to particle score in synovial fluid

Score of particles in synovial fluid	Number of observed cases	Median and range Co ion in whole blood ppb	Median and range Co ion in serum ppb	Median and range Cr ion in whole blood ppb	Median and range Cr ion in serum ppb
0.ABSENT	16	1.4 0.05–4.4	1.5 0.5–6.0	1.2 0.3–4.9	1.7 0.4–11.5
1.PHYSIOLOGICAL	7	6.1 2.2–15.6	8.7 2.5–16.2	2.6 0.7–7.4	4.3 1.0–11.5
2.MILD	6	7.6 5.0–54.3	11.0 5.9–43.6	3.6 0.10–44.5	6.7 0.3–42.8
3.STRONG	11	97.0 23.8–109.6	79.2 18.5–131.0	54.0 10.2–99.3	66.0 8.7–99.2
	Pearson correlation vs. synovial fluid particles score	p=0.8	p=0.8	p=0.7	p=0.7

p-value was considered statistically significant if <0.001

Fig. 2 Cobalt and chromium levels measured in whole blood and serum, according to the score of the particles isolated in synovial fluid. The box represents the median and interquartile range (IQR) and the whiskers represent the range of data excluding outliers (°) and extreme values (*)

In absence of direct determination of the particles in tissues and synovial fluids, other authors have adopted alternative evaluations. For example, De Smet et al. compared the level of circulating Co and Cr ions with the measure of femoral component wear by evaluating the maximum depth of the wear scar in revised MoM hip resurfacing [8]. They found that both serum chromium and serum cobalt levels were strongly correlated with the measure of the femoral component wear. The work comes to the same conclusions as we did, although, being carried out on hip resurfacing, it cannot take into account the corrosion products originating at the taper–trunnion interface.

Bolland et al., instead, examined 17 revised large-bearing hybrid metal-on-metal total hip replacements and found that the high wear at the trunnion-head interface and the passive corrosion of the stem surface are the two main sources of metal ion debris, resulting in high levels of circulating cobalt [27].

Langton et al., in a multicentric study, observed that rates of volumetric wear measured on the surface of revised resurfacings correlated well with serum chromium and cobalt and with particulate tissue load based on optical histology, with no chemical analysis of particles [17].

Davda et al. measured the levels of Co and Cr ions present in the synovial fluid of patients with prostheses without

evaluating the presence of particles; they therefore showed that the analytical method foreseeing acid oxidative digestion causes a significant increase in metal ions measured in the fluid, therefore indirectly proving that nanoparticles are present in the fluid and contribute to the total local content of cobalt and chromium [16].

Concerning the dosage of circulating ions in MoM hip prosthesis, there have been a large number of consistent reports in the literature regarding increased blood metal ions seen after large-diameter MoM articulations [28–32].

High levels of Co and Cr ions can be linked to local reactions in the presence of pseudotumours and aseptic lymphocytic vasculitis-associated lesions (“ALVAL”), which can lead to the destruction of the bone and periprosthetic tissue and therefore to the early loosening of the implant. Langton observed that patients with asymptomatic resurfacing had a median Co of 3.89 in the whole blood, while this was 69 in subjects with adverse reactions to metal debris (ARMD). However, the variability in the two groups of patients is wide, as the ranges are overlapping [17].

Bernstein et al. reported the seven to 13-year clinical, radiographic and metal ion results in patients following MoM THA and found that cobalt and chromium ion levels peaked at four and five years, respectively, and gradually decreased thereafter [33].

On the other hand, as observed by Kwon et al., even in the presence of moderately elevated levels of cobalt and chromium ions (9 ug/L median cobalt serum), the development of pseudotumours detected by ultrasound/magnetic resonance imaging can also be found in asymptomatic patients. On the basis of our experience, such value of circulating Co corresponds to the presence of metal particles in the synovial fluid that can cause the development of the pseudotumour itself [34].

In addition to the local reaction cases, systemic complications from metal ion exposure have been reported, which worsens the whole picture of MoM [13]. Although, at present, there is insufficient data indicating a metal ion threshold as an indicator of periarticular tissue damage and thus a trigger for surgical intervention [35].

This study has certainly some limitations, the main being the semi quantitative evaluation of the Co and Cr particles, this issue cannot be neglected but, no alternative is available at present.

The second limitation is represented by the small number of enrolled patients with a unilateral MoM hip replacement. Nevertheless, the number of available samples was statistically relevant and the statistical analysis revealed a significant correlation between particles isolated in the synovial fluid and the metal ions measured in whole blood and serum samples.

The strength of the present work is that for the first time we demonstrated that there is correlation between debris and circulating ions establishing, in a definitive manner, that the dosage of ions, and in particular of cobalt, can be a surrogate of the direct analysis of the local condition of the prosthesis.

In conclusion, we have demonstrated that the measurement of the Co and Cr ions both in whole blood and in serum can be considered a standard test for screening and monitoring patients with MoM since it is strictly correlated with the release of wear particles and corrosion products at the local level.

Acknowledgments Dr. Milva Battaglia of Diagnostic Sonography of the Rizzoli Institute and orthopaedic surgeons and nursing staff of Prosthetic Surgery and Revisions of Hip and Knee Implants Division for their contribution to samples collection are gratefully acknowledged.

Dr. Lucia Mancini is gratefully acknowledged for her support in revising the manuscript.

This research has been financially supported by Rizzoli Institute and by Ministry of Health, grant RF-2009-1472961.

Conflict of interest The authors declare that they have no conflict of interest.

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