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Original article

Is there a relation between clinical scores and serum ion levels after MoM-THA? One year results in 383 implants

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Summary. *Background and aim of the work:* Adverse reaction to metal debris is the major cause of the high revision rates of metal on metal hip implants with femoral head size ≥ 36mm. Health authorities recommend regular surveillance even for asymptomatic individuals. The main investigations used are Co+ and Cr+ serum levels, x-rays and, eventually, ultrasound and MARS-MRI. Clinic is also assessed. The aim of this study is to identify if there is a relation between ion levels and the clinical scores in order to evaluate the outcome and plan the correct management after this type of implant. *Methods:* 383 subjects were included and divided in 3 groups (serum ion levels >, < and >60 µg/L). Co+, Cr+, HHS and OHS results of 1 year (2017) were analysed in order to show a correlation between ion levels and clinical scores. *Results:* Clinical scores were similar in group 1 and 2. Differences were observed comparing the group 1 and 2 with group 3 for both variables. *Discussion and Conclusions:* Surveillance algorithms have been introduced by health authorities. Nevertheless, the indication to revision surgery is not simple especially in those cases in which a discrepancy between clinic and investigations is present. In this study clinical scores seem to be less important than ion levels in the evaluation of outcomes and in order to plan the correct management in the majority of cases. Larger studies are needed to highlight the real importance of clinical scores in the decision making after these type of implants.

Keywords: hip, prosthesis, metal on metal, ion, clinical scores.

Introduction

Total hip arthroplasty (THA) was first documented in 1891 by Dr. Gluck (1,2) who performed this surgery with an ivory ball and socket affixed with nickel plated screws and it has evolved to become the best surgery of the 21st century (3,4). Great efforts have been made to develop highly wear-resistant materials for bearing surfaces to eliminate or reduce wear and osteolysis after THA.

From the late 1990s to mid-2000s, metal-on-metal (MoM) THA became a popular bearing surface, which at its peak use represented 35% of THA surgeries (5,6).

MoM THAs hoped to obtain an implant that will have improved survivorship because of the lack of wear created from traditional polyethylene bearings. The fluid film lubrication theoretically had to allow the 2 surfaces to slide past each other with minimal contact thereby significantly reducing wear (7,8). Furthermore, the increased head-neck ratio in MoM implants provided increased range of motion, decreased potential for femoral neck impingement, and decreased dislocation rates compared to smaller-head metal on polyethylene (MoP) implants (9,10). Second-generation MoM bearings had initially shown good results both in vitro and in vivo. Metasul MoM bearings (Zimmer, Warsaw, IN) produced a 100-fold lower rate of volumetric wear than a conventional MoP bearing, and Grübl et al. reported a 98.6% survival rate at a minimum 10-year follow-up (11).

In reality, the notion of limited wear due to fluid film lubrication was short lived and it was disproven in 2013 (12). Researchers demonstrated that, during normal walking, there were brief periods of time where contact between the metal surfaces was present, thereby exhibiting boundary lubrication instead of fluid film lubrication. The researchers continued to discuss that during more strenuous hip motions such as ascending and descending stairs up to 36% of the gait cycle was under direct contact, or boundary lubrication, thereby increasing frictional stress at the bone implant interface and any modular components (13,14). This MoM higher wearing and touching increased in head diameters ≥ 36mm and in implant malposition, thus causing an abnormal release of Co+ and Cr+ ions in serum and synovia.

For these reasons, the use of MoM sharply declined (15-17). Increased metal ion concentrations have shown to have local and systemic consequences including direct cytotoxic effects, thereby causing abductor deficiency, capsular attenuation, and bony reabsorption (1). Approximately 10 years after the peak of its use, numerous revisions became apparent because of these adverse reactions to metal debris (ARMD) (18,19). This debris can result in destruction of the local bone and soft tissues, as well as large invasive pseudotumors, which often bring to revision surgery for implant loosening (Figure 1) (18,20).

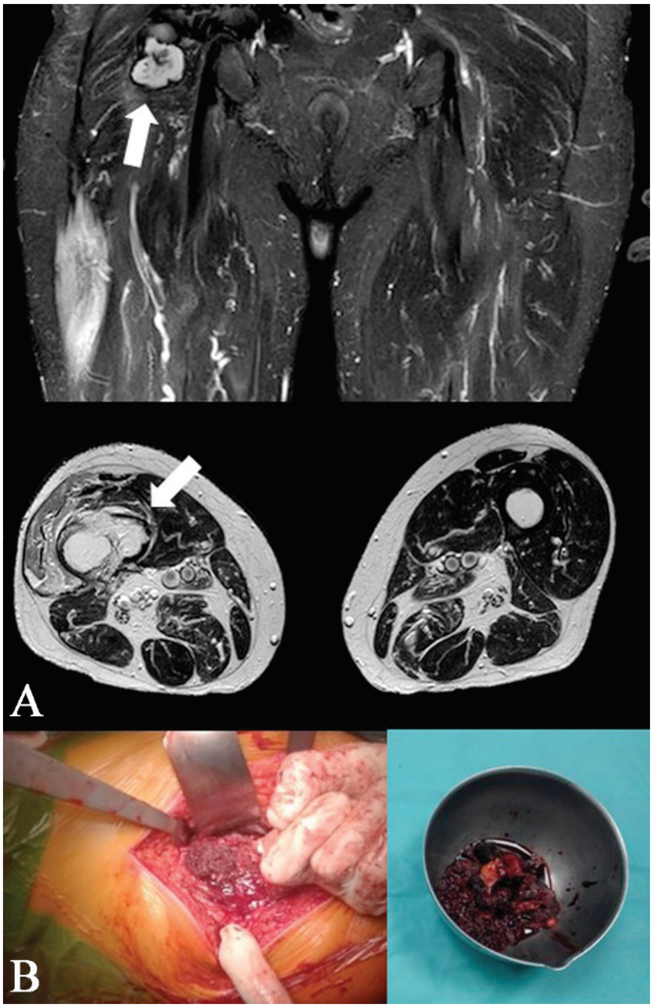

Figure 1. Pseudotumor of the right hip after Mom THA. MARS-MRI with pseudotumor (arrows) (A). Intraoperative views with metallosis (B).

When evaluating a patient with a MoM hip prosthesis, it becomes important to properly review pertinent radiology and lab tests, risk-stratify the patient, and then eventually plan proper surgical intervention. Patients with ARMD may be asymptomatic which can make diagnosis more difficult (18,21), therefore, currently, most MoM THA patients are regularly followed up for life. The main investigations used in surveillance are blood metal ions (Co+ and Cr+ serum levels), conventional radiographs and, eventually, cross-sectional imaging [ultrasound or metal artefact reduction sequence magnetic resonance imaging (MARS-MRI)] (18,22).

When interpreting the results of these investigations pain and functional limitations should be assessed. Patient-reported outcome measures such as the Oxford Hip Score (OHS) and Harris Hip Score (HHS) are reliable and responsive instruments; however, regulatory authorities do not currently provide guidance on clear meaningful thresholds for stratifying MoM THA patients (23).

Few studies in the literature have clearly defined the relation between serum ion levels and functional scores for the operated hip. The aim of this study is to identify if there is a relation between serum ion levels (Cr+ and Co+) and the clinical scores used after a MoM THA in order to evaluate the outcome and to plan the correct management after this type of implant.

Materials and Methods

This study was approved by the local institutional review board and it was proposed by the Emilia Romagna Health Department as part of the national evaluation of MoM THAs program. All included patients signed an informed consent and the study was conducted following the principles of the Declaration of Helsinki. Collected data of 555 patients who underwent primary THA using MoM bearing surfaces between January 2000 and December 2011 were retrospectively reviewed.

Patients older than 60 years of age at the moment of surgery who underwent MoM THAs with head diameter ≥36 mm and without malpositioning in the postoperative x-ray were included; those who were submitted to bilateral THA, hip resurfacing, had previously known renal diseases, died or did not answer to the recall and had BMI>30 were excluded. Proxima Depuy ASR prostheses were also excluded because they were investigated in a previous assessment.

All procedures were performed through a direct lateral approach in the supine position by experienced orthopaedic surgeons with a cement less press-fit technique (Figure 2).

Postoperative rehabilitation was the same in all cases. Partial weight-bearing was allowed with a walker or crutches in the immediate postoperative

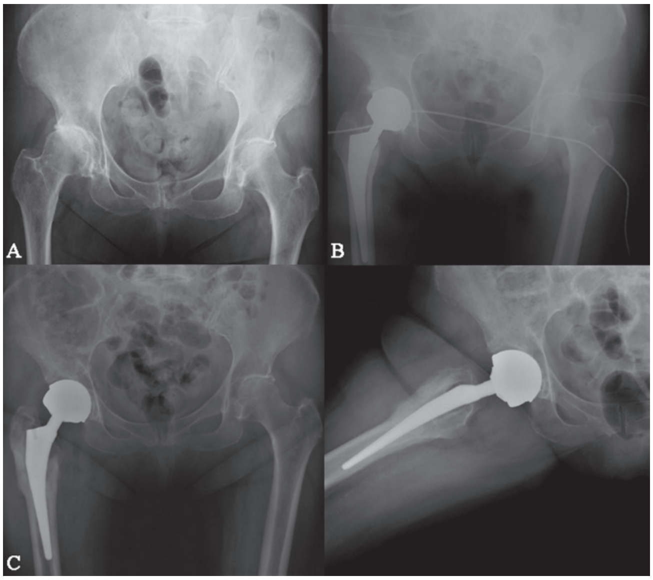

Figure 2. Right hip osteoarthritis. Preoperative x-ray (A), postoperative (B) and 10 years after surgery radiographs (C).

period, and full weight-bearing was allowed as tolerated 6 weeks postoperatively. Patients were clinically and radiographically assessed postoperatively at 1, 3, 6, and 12 months, then annually. Starting from January 2017 all subjects were also recalled in order to undergo to serial blood samples (levels of serum ion Co+ and Cr+), pelvis and hip radiographs and clinical evaluation through Harris (HHS) and Oxford Hip Score (OHS) (23-25). All measurements were performed with an interval of 1 year or 6 months on the basis of the algorithm proposed by the Emilia Romagna Health Department (Figure 3).

Cross sectional imaging (MARS-MRI) was limited to those cases with ion levels (Co+ or Cr+) >7μg/L and <60 μg/L or significant x-rays signs of lysis and/or mobilization confirmed after the first (T0) and second (6 months later T0) evaluation. Revision surgery was indicated with Co+ or Cr+ levels >60μg/L or with cross-sectional imaging positive.

In this study patients were divided in 3 groups:

group 1: serum ion levels <7μg/L

group 2: serum ion levels >7μg/L

group 3: serum ion levels >60μg/L.

Results of 1 year (2017) were analysed. The registered clinical scores were measured for the three groups and related to serum ions levels. Differences were investigated between each group by the Mann- Whitney U test and the independent t-test. Statistical analysis was performed using the SPSS Statistics version 20.0 (IBM Corp., Armonk, NY). Statistical significance was defined as a p value < .05.

Results

After applying the inclusion and exclusion criteria, 383 patients [268 male (69.97%) and 115 female (30,03%)] (mean age of 73±7 years) were enrolled in the study. The minimum follow-up was 5 years (5-17). The etiology of the cohort was primary osteoarthritis (55.9%), osteonecrosis (22.1%), developmental dysplasia of the hip (15%) and post-traumatic osteoarthritis (7.0%). Mean BMI was 26.9 kg/m^2 (range 19–30 kg/m^2).

Group 1 included 330 patients (86,6%), group 2 40 (10,44%) and group 3 13 (3,39%).

All serum analyses were performed by an institutional department of pathology and laboratory medicine, which is specialized in musculoskeletal disorders. The registered clinical scores during follow up in 2017 for the three groups and the serum ion levels are summarized in table 1 and 2. Group 1 and 2 had similar HHS and OHS (p>.05) but different Co+ and Cr+ levels (p=0.03). Instead a statistical significance difference for all parameters was found comparing patients with serum ion levels <60 μg/L (group 1+group 2) and patients with serum ion levels >60 μg/L (group 3) (p=0.001 for Co+ and Cr+) (p=0.013 for HHS)

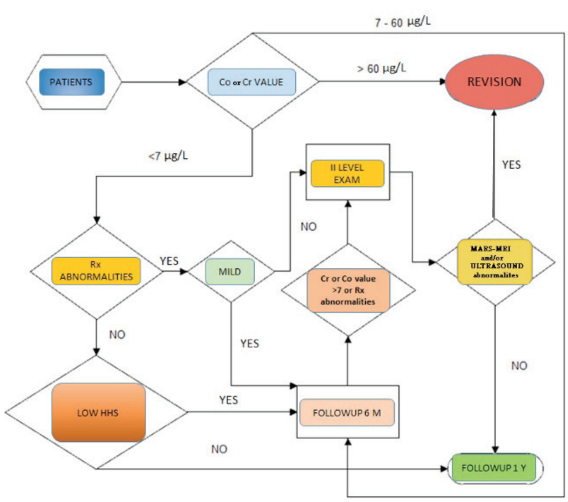

Figure 3. Algorithm proposed by the Emilia Romagna Health Department for MoM THA patients.

Table 1. Mean HHS and OHS in the three groups at follow-up (2017)

	HHS	**OHS**
Group 1	92,11 ± 11,56	32,1 ± 3,05
Group 2	88,65 ± 17,07	31,5 ± 2,65
Group 3	80,75 ± 22,22	25,2 ± 1,36

Table 2. Mean Co+ and Cr+ in the three groups at follow-up (2017)

	Co+	**Cr+**
Group 1	1,30 ± 1,05	1,82 ± 1,12
Group 2	9,07 ± 0,64	9,77 ± 1,05
Group 3	66,63 ± 4,36	68,2 ± 3,36

($p=0.01$ for OHS). Furthermore, all subjects of group 3 had always concomitant significant x-rays changes.

Discussion

Around the turn of the 21th century there was a re-emergence of MoM hip implants. They became a popular bearing surface, which at its peak use represented 35% of THA surgeries (6). The impetus behind MoM use was the hope for longer implant survival due to decreased wear of the bearings compared to the traditional MoP couplings (26). Approximately 10 years after this peak high failure rates have been reported for most large-diameter MoM THA designs (≥ 36mm), which has led to an almost worldwide cessation of their use (27-30). It has been observed that many MoM THA revisions were performed for ARMD (31,32). This metal debris released from the bearing surface and/or other THA modular implant junctions due to wear and corrosion (33-38) can result in destruction of the local bone and soft tissues, as well as large invasive pseudotumors (a specific type of ARMD, defined as a cystic, solid, or mixed mass communicating with the joint) (20,31,33). Unfortunately, patients with ARMD may be frequently asymptomatic and in these subjects a relation between clinical findings and investigations is absent (21,39).

For all these reasons, Health Authorities introduced follow-up algorithms for MoM patients in order to identify early ARMD (22,40,41), but these guidances are not unique. A recent review showed that follow-up protocols issued by 5 worldwide authorities were extremely variable, not evidence-based and very costly (23). The specific role of each investigation performed and clinical assessment is not clear especially in the decision-making to revise the prosthesis.

The main investigations used in surveillance are blood metal ions measurements, conventional radiographs and, eventually, cross-sectional imaging (ultrasound or MARS-MRI) (18,22); in these patients also clinic has to be assessed.

Cobalt and chromium ions are measured because they constitute the primary elements of the MoM alloy. Wear (normal and excessive) and corrosion of MoM THAs causes release of both insoluble metal particles (found in the synovial fluid and periprosthetic tissues) and soluble metal ions (entering the bloodstream thus allowing measurement) (40). Ninety-seven% of healthy subjects have both blood cobalt and chromium concentrations of 2 μg/L or less, with little variation observed between individuals (41). In well-functioning MoM THAs, metal ions can enter the bloodstream by day 5 following implantation (42).

It has been suggested that there is a peak ion concentration in the early phase, followed by a gradual decline and a steady state (43). Until now, little is known about the metal ion concentration levels during the long-term follow-up. Few medium-term or long-term follow-up studies evaluate metal ion levels after

MoM THA with limited number of cases. Savarino et al. (44) reported a minimum 8-year follow-up showing decreasing metal ion concentrations compared with medium-term follow-up for cementless MoM THA, but the study did not evaluate serum metal ion levels sequentially, only measuring the final ion levels. Bernstein et al. (45) also reported an initial peak of metal ion levels at 4 and 5 years postoperatively, gradually decreasing thereafter in their 7- to 13-year follow-up study. The mean follow-up of their cohort was 8.87 years, so it was not truly an annual follow-up of data over 10 years.

Chan et al (46) reported a "run-in wear period" also in their in vitro study. They showed that increased wear occurred within the first 1 million cycles, followed by a marked decrease in rate of wear to lower, steady-state values. An average wear rate of 0.40 mm^3 per million cycles (range, 0.02-1.9) was observed during the run-in period (first million cycles), and once the steady state was reached, an average wear rate of 0.08 mm^3 per million cycles was observed. In this study the minimum follow-up was 5 years and for this reason Authors are confident that serum ion levels are not influenced by peak ion concentration of the early phase.

Predictors of raised blood metal ion concentrations can be divided into patient (female sex, young age, time since implantation, BMI>30), implant (design, small femoral HRA components, large femoral MoM THA components, bilateral MoM THAs), and surgical factors (acetabular component malposition, reduced contact patch to rim distance) (18,20,23,35,47,48). These factors were considered in the design of the study in order to have an homogeneous cohort of cases.

There is presently no international consensus on the acceptable metal ion threshold(s) of concern in MoM THA patients. In this study the threshold of concern was 7 μg/L.

Conventional radiographs provide important information on component position, bone quality, and implant fixation, therefore they can identify signs suggestive of MoM THA failure early (49). However radiographs cannot directly diagnose ARMD or pseudotumors, given that these are predominantly soft-tissue lesions (50). Matharu et al. (51) suggested that radiographic factors predictive of hips with evidence of a pseudotumor included acetabular component malposition (high inclination, and anteversion below 5 degrees), acetabular osteolysis, femoral osteolysis and acetabular loosening. However, it was recommended that radiographs should not be considered a substitute for performing blood metal ions and cross-sectional imaging, given that 20% of HRAs revised for pseudotumors had normal radiographs.

Cross sectional imaging modalities instead are essential for the study of soft-tissue lesions. Ultrasound has frequently been used as the initial imaging modality for investigating MoMHA patients (52). Compared with MARS-MRI, the main advantages of ultrasound include being cheaper (53), faster to perform, not being affected by prosthetic artefacts, and being more accessible with fewer patient contraindications (can be used in patients with pacemakers or those with claustrophobia) (54). Ultrasound also permits dynamic imaging, hip aspirations, and biopsies (54). The main disadvantages of ultrasound include the technique being operator dependent, and difficulties when assessing deeper structures or examining larger patients (54,55). In this study cross sectional imaging was limited to those cases with ion levels (Co+ and Cr+) >7μg/L and <60 μg/L or significant x-rays signs of lysis and/or mobilization confirmed after the first (T0) and second (6 months later T0) evaluation. In those cases in which these second level studies were indicated, Authors always performed MARS-MRI as it is not operator dependent, it provides excellent visualization of soft-tissue structures including deeper tissues, and images can be assessed retrospectively, which is helpful when obtaining further opinions or planning revision (54,56).

When interpreting the results of ion levels and imaging performed in MoM THA patients, pain and functional limitations have also to be considered. Although some studies documented the systemic and local risks related to an increase of metal ion levels no clear relation have been yet established with the functional score of an operated hip. Patient-reported outcome measures such as the Oxford Hip Score (OHS) and Harris Hip Score (HHS) are reliable and responsive instruments; however, regulatory authorities do not currently provide guidance on meaningful thresholds for stratifying MoM THA patients (23). Kalairajah and Murray suggested that an OHS less than 34, or an HHS less than 80 (24,25) could be considered suboptimal patient-reported outcome measures following MoM THA that warrant further investigation. Indeed, a recent large cohort study which developed a clinical scoring system for assessing the risk of revision in 1,434 MoM THAs identified the HHS and blood metal ion levels as the most important predictors of revision. The HHS was subsequently categorized into low risk (80–100), moderate risk (70–79), and high risk (< 70) groups (57).

Unfortunately this study does not confirm these results in those patients with serum ion levels <60μg/L and it is in accordance with the one of van der Veen et al. (58) who reported a similar absence of correlation between serum ion levels and OHS and HHS. Authors believe that these observed data may be due to the low number of cases included (383 vs. 1434). For this reason they also believe that patient-reported outcome measures therefore seem important for risk stratifying MoM THA patients who otherwise may not appear to be symptomatic for surveillance and/or further investigation. On the other hand, in those patients with ion levels higher than 60μg/L, especially if associated with important radiographic variations, this correlation has been observed and it is a further help in giving the indication for revision.

Conclusions

Surveillance algorithms have been introduced by health regulatory authorities. Nevertheless, the indication to revision surgery is not simple especially in those cases in which a discrepancy between clinic and investigations is present. In this study clinical scores seem to be less important than ion levels in the evaluation of the outcomes and in order to plan the correct management in the majority of cases. Larger studies are needed to highlight the real importance of clinical scores in the decision making after these type of implants.

Conflict of Interest: Each Author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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