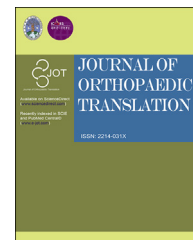




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ORIGINAL ARTICLE

The correlation between activity level, serum-ion concentrations and pseudotumours in patients with metal-on-metal hip articulations and metal-on-polyethylene total hip articulations

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Resurfacing hip arthroplasty;
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Abstract *Purpose:* Young and physically active patients have mainly received metal-on-metal (MoM) total hip arthroplasty (THA) and resurfacing hip arthroplasty (RHA). However, the correlation between daily physical activity (PA) levels, serum-ion concentrations of chromium and cobalt and pseudotumours formation of patients who underwent MoM THA/RHA is insufficiently explored.

Methods: Ninety-nine patients with 134 hip articulations, 71 MoM THA/RHA and 63 MoP THA participated in a cross-sectional study at XXX University Hospital, Denmark, at mean 7.3 (range: 0.4–21.7) years after surgery. Patients' daily PA was monitored during a two-week period using a triaxial accelerometer. Metal artefact reduction sequence magnetic resonance imaging scans, estimation of serum-ion concentrations of chromium and cobalt and the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire were completed on Day 14.

Results: Patients with a pseudotumour who underwent MoM THA/RHA had a higher average cadence of median 101.4 [interquartile range (IQR): 95.5–105] steps/min than patients without a pseudotumour, median 96.7 (IQR: 92.2–103) steps/min ($p = 0.02$). Serum-ion concentrations of chromium and cobalt were higher in patients with a pseudotumour who underwent MoM THA/RHA, median 2.57 (IQR: 1.4–3.4) $\mu\text{g/L}$ and 1.80 (IQR: 1.2–2.6) $\mu\text{g/L}$, respectively, than in

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patients without a pseudotumour, median 1.85 (IQR: 1.1–3.2) $\mu\text{g/L}$ and 1.34 (IQR: 0.9–2.2) $\mu\text{g/L}$ in MoM THA/RHA ($p = 0.04$ and $p = 0.03$). There was no statistical difference in these parameters between patients with and without a pseudotumour who underwent MoP THA. Daily PA levels of patients who underwent MoM THA/RHA were significantly correlated with serum-ion concentrations of chromium ($p = 0.0002$, $r = 0.44$) and cobalt ($p = 0.005$, $r = 0.34$), whereas no correlations were seen among patients who underwent MoP THA ($p > 0.12$).

Conclusion: The daily PA level of patients who underwent MoM THA/RHA influences the serum-ion concentrations of chromium and cobalt and the risk of pseudotumour formation.

Translational potential of this article: Results of this article add important knowledge on potential recommendations of prosthesis selection for patients with a high level of physical activity.

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Introduction

The orthopaedic community had big expectations to the third generation of large-head metal-on-metal (MoM) total hip articulations (THA) and resurfacing hip articulations (RHA) which were considered an excellent treatment option for young and physically active patients for whom the survival of conventional metal-on-polyethylene (MoP) THA was not sufficient [1,2]. However, during 2006–2008, an increasing number of reports revealed that the metal wear debris generated from the bearing surfaces was associated with undesirable side effects such as cystic, mixed and solid pseudotumours [3–5] and high systemic concentrations of cobalt and chromium metal ions [6,7]. Polyethylene wear has been reported to be an outcome of use in patients who underwent MoP THA [8], and it has been hypothesized that increased patient activity might lead to higher metal-ion concentrations in patients who underwent MoM THA/RHA [9,10]. However, information on this topic is limited, conflicting and insufficiently explored in larger study populations with MoM hip articulations. Gleizes et al [11] found a 10% rise in cobalt levels in two patients with Metasul 28-mm bearings after completing 800 m of walking, and two hip simulator studies that imitated “jogging” found a rise in wear rates [12,13]. Furthermore, it was recently reported that patients with the Birmingham Hip Modular Head system who had high University of California Los Angeles activity scores had higher levels of chromium than those with low University of California Los Angeles activity scores [14]. Contrasting, no difference was found in chromium and cobalt levels in seven patients who participated in a high-activity week and a low-activity week [15]. Pseudotumours have been described in patients with increased metal wear debris [16] and high systemic levels of chromium and cobalt [17,18]; however, they have also been found in patients with low systemic levels of chromium and cobalt [19,20]. A deeper knowledge on the correlation between patient activity, metal-ion concentrations and pseudotumour formation would be valuable for orthopaedic surgeons when advising patients with MoM hip articulations on the effect of activity on metal-ion fluctuations and pseudotumour formation. Thus, the primary aim of this

cross-sectional study was to investigate (1) the correlation between patients’ daily physical activity (PA) levels and metal-ion concentrations of chromium and cobalt and (2) the differences in PA parameters between patients with a pseudotumour and patients without a pseudotumour who underwent MoM THA/RHA and MoP THA.

Materials and methods

Patients and articulations

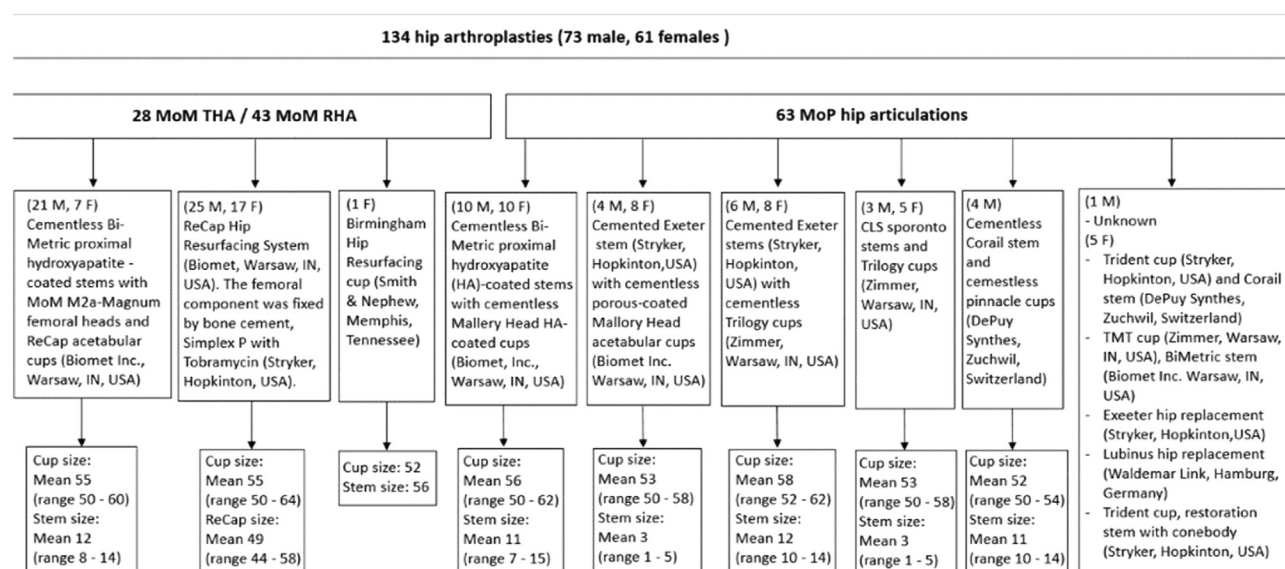
A total of 99 patients with 134 THAs (61 females and 73 males) participated in a cross-sectional study between August 19th and October 17th 2014 at Aarhus University Hospital, Denmark, at mean 7.3 (range: 0.4–21.7) years after surgery. Patients were identified and recruited from five former local research projects on MoM and MoP hip arthroplasties [21–24]. A detailed description of the inclusion and exclusion criteria in each study can be found in the following publications [21–24]. Shortly, the overall inclusion criteria of the five studies were primary osteoarthritis of the hip, acceptable bone mineral density on preoperative dual-energy X-ray absorptiometry (DXA) scan ($T\text{-score} > 1$), age between 18 and 65 years and a written informed consent to participate. The overall exclusion criteria of the five studies were vascular or neuromuscular disease in the operated leg; fracture sequelae; avascular necrosis of the femoral head; women planning pregnancy; alcohol abuse and daily intake of nonsteroidal anti-inflammatory drugs, K-vitamin antagonists or loop diuretics. In the present study, patients were divided into two groups; (1) MoM hip articulations ($n = 71$) (MoM THA ($n = 29$) and MoM RHA ($n = 42$)) and (2) MoP THA ($n = 63$). Descriptive baseline characteristics of all patients and arthroplasties are presented in Table 1 and Figure 1. For insertion of all MoM and MoP THAs, the posterior surgical approach was used. For insertion of the MoM RHAs, either a posterior (ad modum Moore) [25] ($n = 37$) or an anterolateral (ad modum Watson) [25] ($n = 6$) surgical approach was used.

All patients gave informed consent to participate in this study, and all examinations were performed in accordance

Table 1 Descriptive baseline characteristics of patients with metal-on-metal (MoM) total hip arthroplasty (THA)/ resurfacing hip arthroplasty (RHA) and metal-on-polyethylene (MoP) THA.

Articulation	MoM THA/HRA	MoP THA	<i>p</i>
Patients and implants			
Number of patients	71	63	—
Sex (male/female)	46/25	27/36	0.01 ^a
Age at follow-up	59.4 (51.6–64.6)	68.5 (61.2–70.2)	0.0001 ^b
Years since operation	7.4 (4.9–7.9)	8.5 (4.4–11.0)	0.0001 ^b
Implant side, right/left	42/29	28/35	0.92 ^a
Inclination cup angle (°)	43.7 (30.4–57.1)	43.8 (28.9–57.7)	0.93 ^a
Anteversion cup angle (°)	19.1 (4.9–36.9)	23.9 (7.9–44.3)	0.002 ^a
HAGOS			
Symptoms	96.4 (83.9–100)	92.9 (85.7–100)	0.52 ^b
Pain	100 (90–100)	100 (92.5–100)	0.86 ^b
Function in daily living	100 (85–100)	97.5 (85–100)	0.44 ^b
Sport and recreation	98 (75–100)	84.4 (68.8–93.8)	0.12 ^b
Physical activities	87.5 (50–100)	75 (50–100)	0.56 ^b
Hip-related quality of life	95 (67.5–100)	90 (70–100)	0.61 ^b

HAGOS = Hip and Groin Outcome Score.

^a Analysis of variance. Values are represented as mean (range)^b Two-sample Wilcoxon rank-sum (Mann–Whitney) test. Values are median (interquartile range).**Figure 1** Presentation of the different types and brands of hip articulations included in the study.

with the Helsinki Declaration II. The study was approved by the Danish Committee on Biomedical Research Ethics (03.17.2014; jr. nr.: 1-10-72-65-14) and by the Danish Data Protection Agency (02.17.2014; jr. nr.: 2007-58-0010, Trial nr.: 1-16-02-87-14).

Metal artefact reduction sequence magnetic resonance imaging scans

As formerly described [26,27], an MRI protocol with five sequences was used (Table 2) to scan the pelvis and proximal one-third of both femurs. The metal artefact reduction sequence (MARS) magnetic resonance imaging (MRI) scans were performed using two identical 1.5 T Philips Ingenia MRI

scanners (Koninklijke Philips Electronics NV, Eindhoven, the Netherlands), and patients were placed in standardized positions: supine, body parallel with the examination table, feet fixated with a band and first toes pointing towards each other. The MRI scans were assessed on a PACS work station (Agfa Impax, Belgium, version 6.3.1.8000). Two observers evaluated the scans in consensus; one experienced musculoskeletal radiologist (LR) and one PhD student (MHH). The observers were blinded to patients' clinical details, radiographs and serum-ion concentrations.

The Anderson pseudotumour grading system was used to classify pseudotumour findings. This classification has proved the highest intraobserver and interobserver reliability of the currently used systems [28,29]. The Anderson

grading system consists of three categories, A, B and C. Category A is equivalent to “normal or acceptable”, Category B is equivalent to “infection” and Category C is divided into three subgroups: C1 indicates “mild MoM disease”, C2 indicates “moderate MoM disease” and C3 indicates “severe MoM disease”. Besides pseudotumour classification according to the Anderson grading system, we recorded pseudotumour type (fluid/mixed or solid) and anatomical location (anterolateral or posterolateral to the greater trochanter or located to the iliopsoas bursa). Different from the Anderson grading system, patients with a C1 lesion and muscle atrophy or oedema in any other muscles than the short external rotators were not classified as C2 [30].

Assessment of PA

As described in a previous study [27], a commercially available accelerometer (Axiivity, Newcastle upon Tyne, England), which determines the acceleration of body parts in three planes, was used to measure and classify PA. The accelerometer was set to monitor at 100 Hz and ± 8 g. The patients were instructed to wear it during wake hours and to mount the accelerometer on the lateral side on the right thigh with Fixomull tape (3M, USA). The accelerometers were worn for a minimum of 8 h of wear time per day for a

mean of 15 (range: 10–21) days. All accelerometer-based activity data were analyzed by one person. The raw acceleration signal was analyzed using the inclinometer function of the accelerometer and algorithm-based peak detection methods in Matlab (MATLAB R2010a; The Mathworks Inc., Natick, Massachusetts, USA), based on previously published principles [31,32]. Briefly, calibration of the accelerometer’s orientation was performed within a period of level walking, which was manually selected. Within this walking period, the average magnitudes of the three acceleration vectors and the gait cycle frequency (Hz) were derived to allow further differentiation between activities. Differentiation between standing periods and sitting periods was based on the direction of the gravitation vector. Walking was differentiated from other upright activities (all classified as standing) by application of heuristic rules to the gait cycle frequency. A walking period was classified when at least five consecutive heel strike peaks were detected, with 0.6 Hz and 5-min walking bouts. More detailed information of the accelerometer and its clinical application has been described in a previous study [33].

Cup position, serum-ion measurements and clinical outcome scores

At postoperative, mean 7.3 (range: 0.4–21.7) years’ follow-up, standardized, weight-bearing anteroposterior pelvic and lateral hip radiographs were obtained. Cup inclination and anteversion angles were estimated digitally (PolyWare 3D Digital, version 5.10; Draftware Developers, Conway, SC) [34,35]. Blood samples for metal-ion investigations were collected according to the present guidelines [36]. Analyses were undertaken using an inductively coupled plasma–mass spectrometry (ICP-MS) at XXX Hospital, XXX. All patients had normal renal function as determined by serum creatinine levels and estimated glomerular filtration rate. Patients completed The Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire (0–100 scale, where a high score indicates a good outcome) [37]. Patients with bilateral hip articulations completed two questionnaires (one for each hip).

Statistical analysis

Data were checked for normality using the Shapiro–Wilk test combined with Q–Q plot and histograms. Nonparametric data were natural logarithm transformed to allow parametric testing. Logistic regression was used to analyze the effect of the activity parameters on pseudotumour formation. We adjusted for sex, inclination angles and bearing type (MoM THA/RHA) as these variables have been shown to affect serum metal-ion concentrations of chromium and cobalt and pseudotumour prevalence [38–41]. Subanalysis between MoM THA and MoM RHA showed that pseudotumours were present in 9 of 29 (31%) MoM THAs and in 13 of 42 (31%) MoM RHAs. Pearson’s correlation was used to investigate the correlation between activity parameters and serum-ion concentrations of chromium and cobalt. Outcome scores of the HAGOS questionnaire were not normally distributed after natural logarithm transformation, and therefore, the nonparametric two-sample

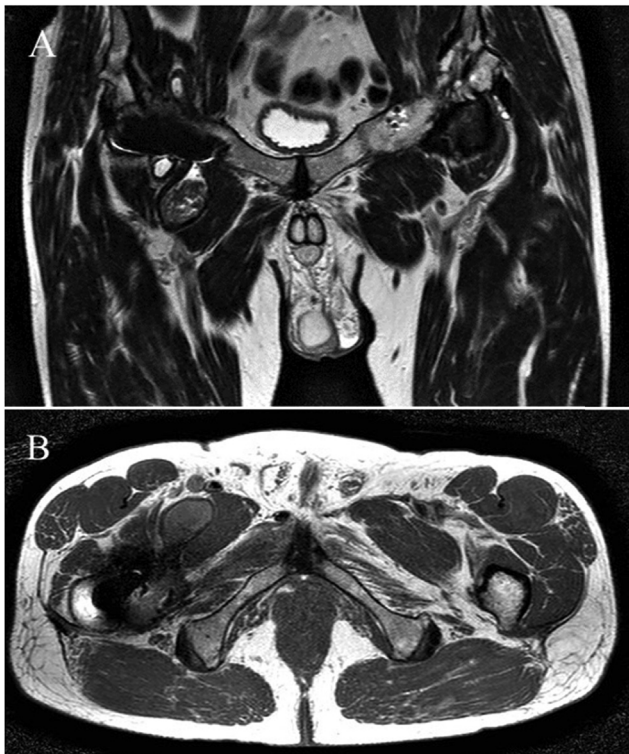


Figure 2 (A) Coronal and (B) axial MARS MRIs of a 54-year-old male with right-side MoM THA (M2a-Magnum, BiMetric Stem) and a mixed pseudotumour located at the iliopsoas bursa. His serum metal-ion levels of chromium and cobalt were 1.4 $\mu\text{g/L}$ and 2.8 $\mu\text{g/L}$, respectively.

MARS = Metal artefact reduction sequence; MoM = metal-on-metal; MRI = magnetic resonance imaging; RHA = resurfacing hip arthroplasty; THA = total hip arthroplasty.

Table 2 Details of magnetic resonance imaging parameters used in this study.

Pulse sequence name	TE (ms)	TR (ms)	TI (ms)	ST (mm) /gab (mm)	FOV	Matrix size	BW (Hz/pixel)	Coil
Coronal T1W MARS	15	450–650	—	2.5/1	360 × 450	380 × 356	438.6	Sense Body 16ch
Coronal STIR MARS	40	4000–8000	130	3.5/1	400 × 454	364 × 320	434.7	Sense Body 16ch
Coronal T2W MARS	80	3000–7000	—	2.5/1	360 × 450	380 × 316	438.6	Sense Body 16ch
Axial T1W MARS	16	450–650	—	2.5/1.5	400 × 454	420 × 348	437.7	Sense Body 16ch
Axial STIR MARS	40	4000–8000	130	3.5/1.5	360 × 447	276 × 272	435.5	Sense Body 16ch

BW = band width; FOV = field of view; MARS = Metal artefact reduction sequence; ST = slice thickness (mm, millimetre); STIR = short tau inversion recovery; TE = time of echo (ms, millisecond); TI = time of inversion (ms, millisecond); TR = time of repetition (ms, millisecond); TSE = turbo spin echo; W = weighted.

Wilcoxon rank-sum (Mann–Whitney) test was used to compare scores between patients who underwent MoM THA/RHA and patients who underwent MoP THA. P-values less than 0.05 were considered statistically significant for the hypotheses tests. All analyses were performed using STATA software, version 13 (StataCorp LP, College Station, Texas).

Results

MARS MRI scans

MRI scans, conventional radiographs and blood samples were obtained from all patients. Accelerometer data from five patients could not be analysed due to technical problems, and 11 patients did not return the HAGOS questionnaire.

MARS MRI evaluations showed that pseudotumours or “MoM disease” were present in 22 of 71 (31%) MoM THA/RHAs and in 25 of 63 (40%) MoP THAs. Mixed or solid pseudotumours were found in two patients who underwent MoM THA (one male and one female) and in eight patients who underwent MoP THA (four males and four females). A detailed description of the MRI evaluations according to the Anderson grading system is presented in Table 3 and Figures 2, 3.

Correlation between PA, serum ions and pseudotumours

Patients with a pseudotumour who underwent MoM THA/RHA had a significantly higher average cadence of median 101.4 (IQR: 95.5–105) steps/min. than patients without a pseudotumour, median 96.7 (IQR: 92.2–103) steps/min. ($p = 0.02$). Patients with a pseudotumour who underwent MoM THA/RHA had significantly higher serum-ion concentrations of chromium and cobalt of median 2.57 (IQR: 1.4–3.4) $\mu\text{g/L}$ and 1.80 (IQR: 1.2–2.6) $\mu\text{g/L}$ compared to median 1.85 (IQR: 1.1–3.2) $\mu\text{g/L}$ and 1.34 (IQR: 0.9–2.2) $\mu\text{g/L}$ in patients without a pseudotumour, respectively ($p = 0.04$ and 0.03) (Table 4). There was no difference in the activity parameters in patients with and without a pseudotumour who underwent MoP THA (Table 4). Daily PA level of patients who underwent MoM THA/RHA was significantly correlated with serum-ion concentrations of chromium ($p = 0.0002$; $r = 0.44$) and cobalt ($p = 0.005$;

Table 3 Results of the MARS MRI evaluations according to the Anderson classification.

Articulation	MoM THA/RHA	MoP THA
Total number of hips	71	63
Total number of pseudotumours	22	25
Grade A “normal or acceptable”	49	38
Grade B “infection”	0	0
Grade C1 “mild MoM disease”	12	14
Male/female	8/4	5/9
Fluid/mixed or solid	11/1	11/2
Location (PL/ILB/AL)	11/0/1	6/8/0
Grade C2 “moderate MoM disease”	9	10
Male/female	8/1	7/3
Fluid/mixed or solid	8/1	5/5
Location (PL/ILB/AL)	7/0/2	5/5/0
Grade C3 “severe MoM disease”	1	1
Male/female	1/0	1/0
Fluid/mixed or solid	1/0	0/1
Location (PL/ILB/AL)	0/0/1	0/1/0

In addition to the Anderson classification, pseudotumour appearance (fluid or mixed/solid) and location were recorded. Location: The anatomical location of the pseudotumour: AL = anterolateral of the greater trochanter; PL = posterolateral of the greater trochanter; ILB = located at the iliopsoas bursa.

MARS = Metal artefact reduction sequence; MoM = metal-on-metal; MoP = metal-on-polyethylene; MRI = magnetic resonance imaging; RHA = resurfacing hip arthroplasty; THA = total hip arthroplasty.

$r = 0.34$), and this relationship was not seen in patients who underwent MoM THA ($p > 0.12$) (Table 5).

Discussion

We investigated the relationship of PA parameters on serum-ion concentrations of chromium and cobalt and pseudotumour formation in a relatively large study population of both patients who underwent MoM THA/RHA and MoP THA. Interestingly, we found significant correlations between patients’ daily PA levels and serum-ion concentrations of chromium and cobalt in patients who underwent MoM THA/RHA, but not in the group of patients who underwent MoP THA. Furthermore, patients with a

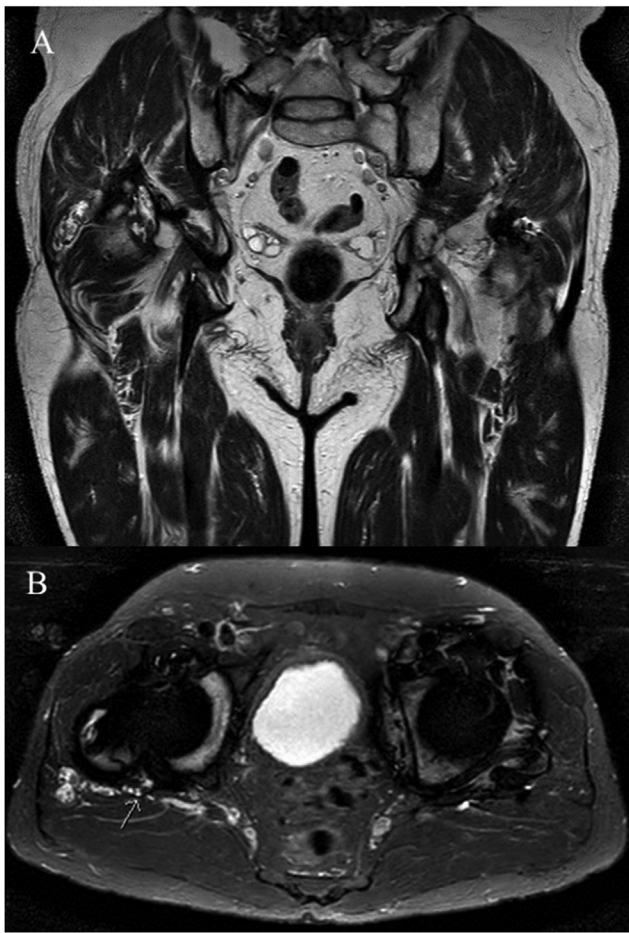


Figure 3 (A) Coronal and (B) axial MARS MRIs of a 64-year-old male with bilateral MoP THA (Right side: Mallory Head, Exeeter Stem, and left side: Pinnacle cup, Corail stem). The pseudotumour on the right side is of mixed type, and on the left side, it is of cystic type.

MARS = Metal artefact reduction sequence; MoP = metal-on-polyethylene; MRI = magnetic resonance imaging; RHA = resurfacing hip arthroplasty; THA = total hip arthroplasty.

pseudotumour who underwent MoM THA/RHA had higher average cadence and higher serum-ion concentrations of chromium and cobalt than patients without a pseudotumour who underwent MoM THA/RHA, and this difference was not present in patients who underwent MoP THA. These results indicate that the daily PA level of patients who underwent MoM THA/RHA influence the serum-ion concentrations of chromium and cobalt and the risk of pseudotumour formation. Information on this topic may be relevant for the orthopaedic surgeon when advising patients with MoM hip articulations on the consequences of activity on serum-ion concentrations and pseudotumour formation—especially because many patients' MoM hip articulations are characterized by a high level of PA.

Previous studies of activity-related changes in serum-ion concentrations of chromium and cobalt after MoM THA or RHA have yielded varying results. An *in vitro* hip simulator study reported a 20-fold increase in metal-ion wear particles when imitating fast jogging compared to normal walking [42].

Similar results have been described in an *in vivo* study by Khan et al [43] who investigated 15 patients with three different MoM bearing types (Birmingham Hip Resurfacing, Cormet 2000 resurfacing and Metasul THA) and found that 1 h of running or fast walking on a treadmill resulted in a mean rise of serum chromium of 11% and of serum cobalt of 13%.

In contrast, Heisel et al. monitored seven patients with MoM hip articulations at 7 to 25 months postoperatively during a two-week period; in the first week, patients were instructed to limit their activity levels, and the next week, patients were encouraged to raise their activity levels, and they completed a 1-h treadmill test. However, no significant differences were found in mean serum cobalt and chromium levels between the low-exercise week (cobalt, 1.4 ppb; SD, 0.85; chromium, 2.08 ppb; SD, 0.9) and the high-exercise week (cobalt, 1.29 ppb; SD, 0.63; chromium, 2.12 ppb; SD, 0.87) [15]. In addition, a triathlete with a Birmingham hip resurfacing hip articulation had his serum-ion concentrations of chromium and cobalt, and urine chromium measured seven days before, during and after a triathlon race. There was no significant change in serum-ion concentrations of chromium or cobalt, but urine chromium levels were significantly elevated immediately after and until 6 days after the race [44]. It is complex to provide an exact clarification for these different findings. However, differences in the analytical serum-ion measurement techniques might play a role. Our study and the study by Khan et al. used inductively coupled plasma–mass spectrometry (ICP-MS), which has a detection limit of 0.02 µg/L for chromium and 0.005 µg/L for cobalt in serum [45], whereas Heisel et al [15] used graphite furnace atomic absorption, which has a detection limit of 0.03 µg/L for chromium and 0.3 µg/L for cobalt in serum. Furthermore, De Hann et al collected their blood samples on the day after the race, by which time the metal ions could have returned to their preexercise levels and thus biased the results. One limitation of the aforementioned studies was small study populations (15, 7 and 1 patient). However, because we investigated 71 MoM hip articulations, our results add strength to the hypothesis that the activity level in patients with MoM hip articulations does influence serum-ion concentrations of chromium and cobalt. Furthermore, the validity of our findings in MoM THA/RHA patients was supported by the insignificant correlations between activity levels and serum-ion concentrations of chromium and cobalt found in patients who underwent MoP THA.

All bearing surfaces experience some degree of wear debris. The dominant source of wear debris in MoM THA/RHA origins from the cobalt–chromium alloy bearing [46]. In THA, corrosion at the taper–trunnion junction also plays a significant role in the generation of metal-ion wear debris [47–49]. This leads to elevated serum-ion concentrations in MoM THA compared to MoM RHA [50,51] and may also lead to high serum-ion concentrations and soft-tissue reactions with pseudotumours in MoP THA [52–55]. We observed pseudotumours in 22 of 71 (31%) patients who underwent MoM THA/RHA and in 25 of 63 (40%) patients who underwent MoP THA. Patients with a pseudotumour who underwent MoM THA/RHA had significant higher serum-ion concentrations of chromium and cobalt and a higher average cadence than patients without a pseudotumour. Former studies have additionally described pseudotumours

Table 4 Differences in activity parameters and serum ions of chromium between patients with a pseudotumour and patients without a pseudotumour.

Output	Pseudotumour	Nonpseudotumour	<i>p</i> ^a
MoM THA/RHA			
Average cadence (steps/min)	101.4 (95.5–105)	96.7 (92.2–103)	0.02
All activities ^b (%)	41.3 (36.2–46.9)	37.8 (29.3–48.4)	0.26
All inactivities ^c (%)	56.8 (53.1–63.7)	58.8 (51.5–70.7)	0.54
Walking time (%)	12.1 (11–15)	10.8 (8.9–13.8)	0.26
Bicycling time (%)	0.45 (0.2–1.6)	0.20 (0.1–0.36)	0.09
High-impact activity (%)	0.02 (0.001–0.14)	0.005 (0.001–0.01)	0.08
Sitting or lying down (%)	56.8 (53.1–63.7)	58.8 (51.5–70.7)	0.54
Standing time (%)	27.5 (21.7–30.4)	25.6 (19.7–34.8)	0.41
Chromium (µg/L)	2.57 (1.4–3.4)	1.85 (1.1–3.2)	0.04
Cobalt (µg/L)	1.80 (1.2–2.6)	1.34 (0.9–2.2)	0.03
MoP THA			
Average cadence (steps/min)	93.4 (89.2–99.6)	95.7 (90.7–103.3)	0.30
All activities ^b (%)	41.2 (36.7–45.7)	38.3 (29.9–47.4)	0.32
All inactivities ^c (%)	57.7 (54.3–63.3)	58.5 (52.5–70.2)	0.79
Walking time (%)	12.0 (9.5–15.6)	11.3 (9.0–15.9)	0.51
Bicycling time (%)	0.40 (0.14–1.82)	0.12 (0.14–0.92)	0.05
High-impact activity (%)	0.01 (0.00–0.04)	0.01 (0.00–0.28)	0.70
Sitting (%)	57.7 (54.3–63.3)	58.5 (52.5–70.2)	0.79
Standing time (%)	27.4 (23.1–29.2)	25.4 (19.4–35.1)	0.32
Chromium (µg/L)	0.75 (0.59–0.72)	0.86 (0.59–1.16)	0.34
Cobalt (µg/L)	0.75 (0.59–0.65)	0.95 (0.59–0.67)	0.12

MoM = metal-on-metal; MoP = metal-on-polyethylene; RHA = resurfacing hip arthroplasty; THA = total hip arthroplasty.

^a Logistic regression (adjusting for risk factors of sex, inclination angle and the type of arthroplasty in the MoM THA/RHA group). Values are represented as median (interquartile range).

^b All activities defined as walking, standing, bicycling and high-impact activity

^c All inactivities defined as sitting and lying down

in patients with high levels of metal wear debris [16] and high systemic levels of chromium and cobalt metal ions [17,18]. However, pseudotumours have also been described in patients with low systemic levels of chromium and cobalt metal ions [19,56]. These conflicting results might be due to various blood sampling procedures (e.g., specimen collection, processing, analysis and storage) and various definitions of pseudotumours and pseudotumour-grading systems [19,29,56–58], which makes it difficult to compare results between studies directly.

In MoP THA, it has been shown that patients with high polyethylene wear rates (mean, 0.134 mm/year) have a 17% higher average cadence than patients with low polyethylene wear rates (mean, 0.047 mm/year) [59]. This is similar to our results of the patients with a pseudotumour who underwent MoM THA/RHA, who had a significant higher average cadence along with higher serum-ion concentrations of chromium and cobalt, compared to patients without a pseudotumour who underwent MoM THA/RHA.

We recognize the limitations of our study. First, the study was limited by the relatively small sample size investigated. Second, we did not monitor fluid output and intake, and patients might have been dehydrated or overhydrated at the time point of blood sampling. Third, the two groups were not matched and different in anteversion angle, time since operation and age. However, because there was no difference between groups in the HAGOS score, we believe that patients had similar physical capacity.

Finally, patients did not follow an activity protocol, and it is uncertain whether an acute increase in activity or longer changes in activity would have affected the serum-ion concentrations. However, the aim of the study was to measure patient's daily PA levels in an uncontrolled environment, and just four days of activity monitoring has been shown to reflect the general activity level of individuals [60].

Conclusion

Our results suggest that the daily PA levels of patients who underwent MoM THA/RHA influence the serum-ion concentrations of chromium and cobalt and the risk of pseudotumour formation. At the same time, we do not neglect that other factors such as implant orientation, head size, clearance, edge loading, manufacturing process, type of coating, shell thickness, use of adaptor sleeve and the female gender may also play a role. Nevertheless, our results add new and important knowledge to the literature and valuable information for the orthopaedic surgeon when advising patients with MoM hip articulations on the consequences of activity on serum-ion concentrations of chromium and cobalt and pseudotumour formation—especially because many patients were selected to undergo MoM hip arthroplasty due to their high activity level.

Table 5 Correlations between accelerometer variables and values of chromium and cobalt in all patients. Estimates are Pearson's r (p -value).

AM parameters	Cobalt, Pearson's r (p -value)	Chromium, Pearson's r (p -value)
MoM THA/RHA		
Average cadence (steps/min)	0.02 (0.89)	0.08 (0.54)
All activities ^a (%)	0.34 (0.005)	0.44 (0.0002)
All inactivities ^b (%)	-0.35 (0.004)	-0.44 (0.0002)
Walking time (%)	0.22 (0.08)	0.30 (0.01)
Cycling time (%)	0.11 (0.40)	0.14 (0.28)
High-impact activity (%)	0.03 (0.88)	-0.09 (0.60)
Sitting (%)	-0.35 (0.004)	-0.44 (0.0002)
Standing time (%)	0.31 (0.01)	0.44 (0.001)
MoP THA		
Average cadence (steps/min)	-0.01 (0.99)	-0.44 (0.75)
All activities ^a (%)	-0.19 (0.15)	-0.13 (0.32)
All inactivities ^b (%)	0.15 (0.27)	0.09 (0.51)
Walking time (%)	-0.07 (0.59)	-0.13 (0.33)
Cycling time (%)	-0.21 (0.45)	-0.14 (0.32)
High-impact activity (%)	-0.10 (0.15)	0.07 (0.61)
Sitting (%)	0.15 (0.27)	0.09 (0.51)
Standing time (%)	0.34 (0.12)	0.02 (0.94)

AM, accelerometer; MoM = metal-on-metal; MoP = metal-on-polyethylene; RHA = resurfacing hip arthroplasty; THA = total hip arthroplasty.

^a All activities defined as walking, standing, cycling and high-impact activity.

^b All inactivities defined as sitting and lying down.

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Conflict of interest

None of the authors have financial or institutional disclosures to report related to the research in this article.

Authors' contributions

M.H., M.S., I.M., L.R. and K.S. were involved in the follow-up examinations. M.H., I.M. and M.S. performed the statistical analyses and interpretation. M.H. wrote the initial manuscript, and M.S., I.M., L.R. and K.S. helped revise it. All authors approved the final manuscript.

Ethical approval and informed consent

All patients gave informed consent to participate in this study, and all examinations were performed in accordance with the Helsinki Declaration II. The study was approved by the Danish Committee on Biomedical Research Ethics (03.17.2014; jr. nr.: 1-10-72-65-14) and by the Danish Data Protection Agency (02.17.2014; jr. nr.: 2007-58-0010, Trial nr.: 1-16-02-87-14).

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