

No association between pseudotumors, high serum metal-ion levels and metal hypersensitivity in large-head metal-on-metal total hip arthroplasty at 5–7-year follow-up

Mette Holm Hjorth¹ · Maiken Stilling¹ · Kjeld Soballe¹ · Lars Hans Bolvig² · Jacob Pontoppidan Thyssen³ · Inger Mechlenburg¹ · Stig Storgaard Jakobsen¹

Received: 4 September 2015 / Revised: 21 September 2015 / Accepted: 28 September 2015 / Published online: 10 October 2015
© ISS 2015

Abstract

Objective The relationship between metal wear debris, pseudotumor formation and metal hypersensitivity is complex and not completely understood. The purpose of this study was to assess the prevalence of pseudotumor formation in a consecutive series of metal-on-metal (MoM) total hip arthroplasty (THA) and to investigate its relationship to serum metal-ion levels and hypersensitivity to metal.

Methods Forty-one patients (31 males), mean age 52 (28–68) years, with a total of 49 large-head MoM THA participated in a 5–7-year follow-up study. Patients underwent ultrasonography, serum metal-ion concentrations were measured, metal allergy and atopic dermatitis were evaluated, and the

questionnaires of the Oxford Hip Score (OHS), Harris Hip Score (HHS) and the Short-Form Health Survey (SF-36) were completed.

Results Pseudotumors were found in eight patients, but they were asymptomatic and their serum metal-ion levels were similar to those observed in patients with no pseudotumors ($p>0.36$). The capsule-stem distance of mean 8.6 mm (SD 3.82, 95 % CI: 5.40–11.79) was wider ($p=0.02$) in patients with pseudotumours than in patients without pseudotumors of mean 5.6 mm (SD 2.89, 95 % CI: 4.68–6.58). Positive patch test reactions were seen in three patients. Higher serum metal-ion levels of chromium and cobalt were significantly correlated with steeper cup inclination and smaller femoral head sizes, and were associated with female gender ($p<0.04$).

Conclusion We found no association between pseudotumor formation, serum metal-ion levels, metal patch test reactivity, and atopic dermatitis. However, clinicians should be aware of asymptomatic pseudotumors, and we advise further exploration into the mechanisms involved in the pathogenesis of pseudotumors.

Keywords Large-head MoM THA · Ultrasonography · Pseudotumor · Serum metal-ion levels · Metal hypersensitivity

✉ Mette Holm Hjorth
mettehh20@gmail.com; <http://www.OrthoResearch.dk>

Maiken Stilling
maiken.stilling@ki.au.dk

Kjeld Soballe
kjeld@soballe.com

Lars Hans Bolvig
larshans@rm.dk

Jacob Pontoppidan Thyssen
jacob.p.thyssen@regionh.dk

Inger Mechlenburg
inger.mechlenburg@ki.au.dk

Stig Storgaard Jakobsen
stig.jakobsen@ki.au.dk

¹ Department of Orthopaedics, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark

² Department of Radiology, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark

³ Department of Dermato-Allergology, Gentofte Hospital, University of Copenhagen, Hellerup, Copenhagen, Denmark

Introduction

There is great concern regarding metal release from metal-on-metal (MoM) total hip replacements. In large-head MoM total hip arthroplasty (THA), suspected culprits are nano-sized metal wear particles generated from the articulating surfaces and corrosion from the bearing surfaces, wear particles, and taper junction [1–3]. The metal wear particles are spread locally as well as systemically and are associated with metallosis, cystic, solid or semisolid pseudotumors [4, 5], and have

histologically been described as “aseptic lymphocytic vasculitis associated lesions” (ALVALs) [6]. An umbrella term “adverse reaction to metal debris” (ARMD) is used to cover these unexpected and undesirable side effects associated with MoM hip articulations [7]. To detect pseudotumor formation, the British Medicines and Healthcare Products Regulatory Agency [8] and the American Hip Society [9] recommend a variety of clinical and diagnostic parameters. These recommendations include the use of cross-sectional imaging with metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI), computed tomography (CT), or ultrasonography (US). Ultrasonography assessment of MoM hip articulations has some advantages over MRI and CT assessments. These advantages include absence of ionizing radiation, absence of implant-induced metal artifacts and low cost [10]. Pseudotumor formation has been described in both asymptomatic and symptomatic patients [11–13] as well as in patients with low metal ion levels and well-positioned cups [14, 15]. The effect of excess wear and patient-specific sensitivity to the metal wear debris in the etiopathogenesis of pseudotumors remains unclear, and it appears that different patients might have different responses to the metal wear debris. Metal allergy is a suspected cause of pseudotumors, and it has been found that 81 % of patients with failed MoM hip articulation were metal-sensitized [16]. This suggests that metal hypersensitivity may be a contributing factor to failure of MoM hip articulations.

Furthermore, individuals with atopic dermatitis have been shown to exhibit cutaneous, delayed-type hypersensitivity to nickel, cobalt, and chromium allergens more often than individuals without atopic dermatitis [17]; however, there is a lack of knowledge of the true prevalence of metal hypersensitivity to orthopedic implants, the association between cutaneous and deep implant sensitivity, and the exact role of hypersensitivity in the pathogenesis of pseudotumors. We hypothesized that patients with a pseudotumor would have higher serum metal-ion levels and a higher prevalence of metal hypersensitivity than patients without a pseudotumor. The aim of this 5–7-year follow-up study was therefore to perform US examination in a consecutive series of large-head MoM THA and to investigate the potential association between pseudotumor formation, serum metal-ion levels, metal allergy, and atopic dermatitis. Another aim of the present study was to assess patients’ self-reported hip function and health-related quality of life.

Material and methods

Study design, prosthesis and patients

A consecutive series of 41 patients below 65 years at the time of surgery and diagnosed with either osteoarthritis, hip dysplasia sequelae, or caput necrosis underwent large-head MOM

THA between August 2006 and October 2007. Excluded were pregnant women due to a potential risk of transferring metal-ions to the embryo, and patients that were included were in another ongoing research project at the department.

Three experienced orthopaedic surgeons undertook all operations using a posterolateral approach. All patients received cementless Bi-Metric proximal HA-coated stems with M2a-Magnum femoral heads and ReCap acetabular solid shells (Biomet Inc., Warsaw, Indiana, USA). The ReCap acetabular press-fit cup and the M2a-Magnum head are made of an “as-cast” high-carbon cobalt chromium molybdenum (CoCrMo) alloy. The system is modular at the head-neck junction. The head size is dependent upon the cup size and the neck length is adjusted via adaptors inserted into the femoral head. The outer diameter of the ReCap cup is fully hemispherical (180°) with four rim indentations for the stable attachment of the locking impaction device. It is 6 mm thick at the dome and its thickness at the rim averages 3 mm, while the radial clearance level of the M2a-Magnum articulation is maintained at 75–150 μm [18]. The stem and taper are made of a titanium, aluminium, and vanadium alloy (TiAlV); and lateralized stems have an increased taper and trunnion length. After surgery, patients were instructed to walk with full weight-bearing gait, but with movement restrictions regarding flexion, adduction, and internal rotation for the first 6 weeks; thereafter, no restrictions were placed on movement. Two patients had post-operative complications; one suffered a superficial infection, which was treated with I.V. antibiotics (Dicloxacilline), and the other patient suffered transient ischial nerve infection.

In July–August 2012, we performed a 5–7-year follow-up examination of all 41 patients/49 hips (31 male patients/38 male hips), mean age 52 (28–68) years. Eight patients had bilateral M2a-Magnum articulations, while another five had bilateral MoM hip articulations of different types and brands—three resurfacing hip THAs (two ReCap; Biomet Inc. and one Birmingham Resurfacing Hip), one metal-on-ceramic THA (DePuy) and one MoP THA (Biomet Inc.).

The 5–7-year follow-up included US scans of all hip joints, fine-needle US-guided aspiration of masses when possible, measurement of serum metal-ion concentrations (chromium and cobalt), evaluation of metal allergy assessed by patch testing and a questionnaire, scores of hip function by the Oxford Hip Score (OHS) [19] and the Harris Hip Score (HHS) [20], and scores of health-related quality of life by the Medical Outcomes Study Short Form 36 (SF-36) [21]. All patients gave informed consent to participate in this study. The follow-up examinations were performed in accordance with the Helsinki Declaration II, and the study was reported to and reviewed by the local ethical committee (inquiry 86/2012, 05.31.2012). The collection of data was approved by The Danish Data Protection Agency, 06.27.2012, journal No.: 2007-58-0010, trial No.: 1-16-02-151-12.

US scans

US examinations were performed by two experienced musculoskeletal fellowship-trained observers with 10 and 30 years of experience, respectively. The examinations were performed between July and December 2012. We used either a Hitachi Hi vision Preirus 2012 scanner or a Hitachi Ascendus 2012 scanner. Both scanners had an 8–14-MHz linear transducer and a 2–5-MHz curved transducer which were used in both the longitudinal and transverse planes. Where appropriate, the highest possible frequency was applied to provide adequate penetration. All examinations were made in a standardized manner using a systematic scanning technique as follows:

1. *Anterior examination.* The hip joint was scanned with the patient in the supine position and a mild external rotation of the hip. The anterior synovial recess was identified by placing the transducer parallel to the femoral neck (oblique angle 45°). The fluid effusion that anteriorly displaces the joint pseudocapsule from the anterior cortex of the femoral neck component of the hip prosthesis was quantified (Fig. 1) in all patients as this distance has been associated with metal particle disease [22, 23]. Scans in the longitudinal and axial planes were used to examine the iliopsoas muscle, tendon, and bursa.
2. *Lateral examination.* Patient in the lateral position: longitudinal and axial scans of the greater trochanter were obtained to examine the trochanteric bursa for fluid collection and the tendinous attachment of the gluteus medius muscle.
3. *Posterior examination.* The posterior aspect of the greater trochanter and the posterior part of the hip joint was scanned with the patient in lateral position: axial scans were used to examine the gluteus maximus muscle for soft-tissue lesions. Posterior scans were performed; we initially used the linear transducer and thereafter the curved transducer. The curved transducer allowed for a deeper, but less detailed image of the soft tissue and the bony and implant contours. In thin patients, it was possible to obtain a deep posterior image with the linear, more detailed transducer. In compliance with two previous studies [11, 24], we defined a pseudotumor as a solid or cystic periprosthetic soft tissue mass that could not be attributed to an infection, malignancy, bursa, or scar tissue. A thickened pseudocapsule was not considered a pseudotumor. During each scan, the surrounding soft tissues were visualized in all positions to identify the presence of pseudotumors. In presence of pseudotumors, US-guided needle aspiration was attempted. If the aspiration did not succeed, we did not proceed with a needle biopsy because this procedure involves a higher risk of infection [25]. Thus, we assumed that pseudotumors that could not be aspirated were non-fluent. Aspiration was performed

under a sterile procedure with the transducer covered, a sterile field, sterile gel, and the radiologist was wearing sterile gloves. Fluids were investigated for infection with prolonged cultivation for *Propionibacterium acnes* [26]. The joint fluid was collected in Trace Element Serum 6.0 ml (13×100 mm) KFK359 tubes (REF 368380; Becton Dickinson, Franklin Lakes, NJ, USA) [27] for analysis of chromium and cobalt and stored at −80 °C until all US scan had been performed. Samples were examined by inductively coupled plasma mass spectrometry (ICP-MS) at Vejle Hospital, Denmark. The two US observers (L.H.B. and N.B.) were blinded to the clinical findings, the patch test results, and the measurements of serum metal-ion concentrations of chromium and cobalt.

Metal allergy and atopic dermatitis

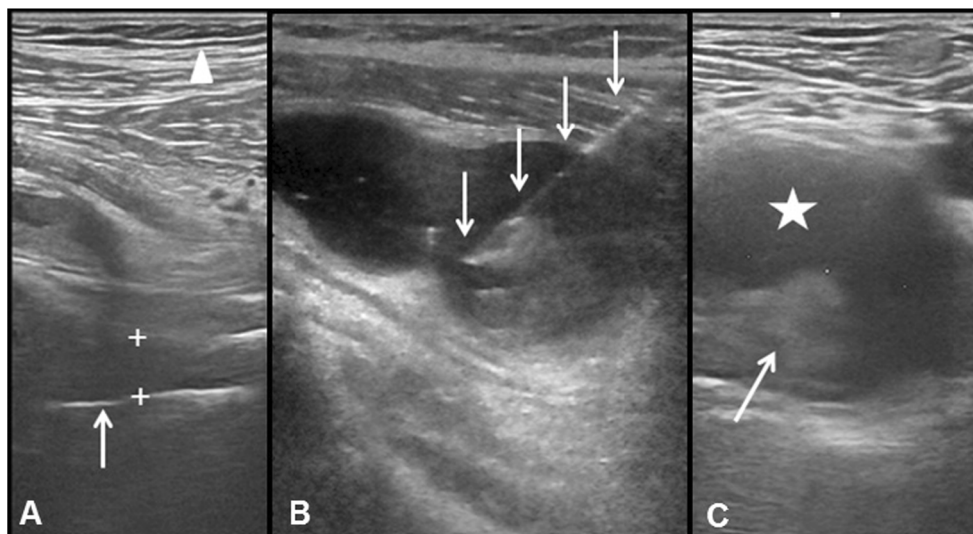
Patch test

Patch testing was performed with Finn Chambers® (8 mm; EpitestLtdOy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Alpharma, Vennessla, Norway). Patch test ingredients were from Hermal®, Reinbek, Germany and Chemotechnique, Malmö, Sweden and included Ferric Chloride 2 %, aluminum chloride hexahydrate 2 %, vanadium(III) chloride 1%, potassium dichromate 0.5 %, nickel sulphate 5 %, manganese chloride 2 %, titanium dioxide 10 %, zirconium(IV) Chloride 1 %, molybden (V) chloride 2.5 %, and cobalt(II) chloride hexahydrate 1 % in pet. Patch tests were applied on the upper back, and patients were instructed to remove the patches 48 h after application. Following another 48 h, skin reactions were evaluated in the patient's home according to the criteria from the International Contact Dermatitis Research Group (ICDRG); thus, homogeneous erythema and infiltration in the entire test area were scored as a 1+ reaction. Homogeneous erythema, infiltration, and vesicles in the test area were scored as a 2+ reaction. Homogeneous erythema, infiltration, and coalescing vesicles in the test area were scored as a 3+ reaction. 1+, 2+, and 3+ readings were interpreted as positive responses. Irritant, doubtful, and negative readings were classified as negative test reactions. The patch test results were photographed and secondarily reviewed by a dermatologist (J. P. T.) with experience in patch testing.

Questionnaire

All patients completed a questionnaire including questions on previous metal allergies and metal exposures. These included: “Have your ears been pierced?”, and “Have you ever experienced dermatitis following skin exposure to jewelry, buttons,

Fig. 1 **a** Illustration of a capsule-stem distance (illustrated by the two crosses) of 8.6 mm. The metallic femoral neck is seen above the arrow. The arrow-head at the top shows the fascia between the muscular layer and the subcutaneous fat tissue. **b** Fine-needle aspiration of a cystic pseudotumor, the needle is marked with arrows. **c** A cystic pseudotumor (star) with a solid component (arrow)



and watches?”, and information on post-operative changes or progression in hypersensitivity symptoms such as urticaria, dermatitis, erythema, and itching around the hip was assessed by the following questions “Have you experienced a postoperative, subsequent redness around the operated hip?”, and “Have you experienced postoperative progress in hypersensitivity?” [28, 29]. A history of atopic dermatitis was assessed by an affirmative response to the following question “Have you ever experienced dermatitis in the creases of the knees and elbows?”

Serum metal-ion measurements

At the 5–7-year follow-up, blood samples were collected according to recent guidelines [30]. In each case, the first three samples were used for other blood examinations to avoid chromium contamination from the steel needle [31, 32]. The blood was collected in Trace Element Serum 6.0 ml (13 × 100 mm) KFK359 tubes (REF 368380; Becton Dickinson, Franklin Lakes, NJ, USA) [27]. All blood samples were examined by ICP-MS at Vejle Hospital, Denmark. Serum levels of leucocytes, C-reactive protein (CRP), creatinine, and glomerular filtration rate (GFR) were also analyzed to screen for infection and renal impairment. All patients returned a questionnaire about possible work or leisure-related chromium or cobalt exposures. Questions were asked regarding oral intake of minerals, tattoos, profession or past-time activities that involved cement, pottery glaze or metal.

Radiographs, clinical outcome of hip function and general health

At the 5–7-year follow-up, standardized weight-bearing anterior-posterior pelvic and lateral hip radiographs were obtained.

Cup inclination and cup anteversion were measured digitally (PolyWare 3D Digital version 5.10; Draftware Developers, Conway, SC). All analyses of cup positions were repeated, and the mean of the first and the second assessment was used. There was no difference between the two repeated measurements in either cup inclination ($p=0.85$) or cup anteversion ($p=0.53$). The postoperative and 5–7-year radiographs were evaluated in consensus by two observers. The following parameters were evaluated: signs of osteolysis around the cup [33] and stem [34], heterotopic ossification (classified according to Brooker) [35], cup migration, and stem subsidence. At the 5–7-year follow-up, hip function was assessed by the HHS [20] (range; 0–100) and the OHS (range; 0–48), and health-related quality of life was assessed by the (SF-36) (range; 0–100) [21]. The SF-36 consists of 8 domains: physical functioning, social functioning, physical role, emotional role, mental health, vitality, bodily pain, and general health perception.

Statistical analyses

All continuous variables were tested for normality (Shapiro-Wilk test) [36]. When data were normally distributed, we used the Student’s *t*-test (Satterthwaite); and when not normally distributed, we used the non-parametric tests (Mann-Whitney *U*-test and Wilcoxon rank-sum) to compare the means. Categorical variables were tested using the Chi-square test or Fischer’s exact test as appropriate. Calculations of the correlation coefficient (*r*) of independent variables were made using Spearman or Pearson correlation analysis as appropriate. *P*-values less than 0.05 were considered statistically significant for the tests of the hypotheses. All analyses were performed using STATA 11.1. (StataCorp LP, College Station, Texas).

Results

No components had been revised after 5–7 years of follow-up. Two patients (one double hip) did not show up for US examination and one patient declined the invitation to undergo patch testing. This left us with serum metal-ion measurements from 41 patients, US scan examinations from 39 patients/46 hips, patch tests from 40 patients, questionnaires on hip function from 49 hips, and questionnaires on health-related quality of life and metal hypersensitivity from 41 patients.

US scans

At the 5–7-year follow-up, eight patients were diagnosed with a pseudotumor of whom one had two separate pseudotumors around one hip joint. This left us with a total of nine pseudotumors in 46 hips (19.5 %). It was possible to perform US-guided aspiration in five (56 %) pseudotumors, but not in the remaining four (44 %) as the US observed mass could not be aspirated using a fine needle (detailed description in Table 1). Infection and growth of *Propionibacterium acnes* was excluded in all cases. While patients with a pseudotumor had a statistically significantly wider capsule-stem distance of mean 8.6 mm—standard deviation (SD) 3.82, 95 % CI: 5.40–11.79 vs. mean 5.6 (SD 2.89, 4.68–6.58) ($p=0.02$)—they did not have higher serum metal-ion levels of chromium ($p=0.89$) or cobalt ($p=0.63$); however, the capsule-stem distance was significantly correlated with serum metal-ion levels of chromium and cobalt (Table 2; Fig. 2). Seven patients presented with a pseudotumor in a posterior-lateral position. Within this group, it appeared that three of the pseudotumors arose from the hip joint. Two patients had an anterior cystic pseudotumor, which appeared to involve the psoas bursa. No patients with bilateral prostheses had pseudotumors, and no patients had muscle abnormalities. One patient (Table 1, patient no. 2) had two separate pseudotumors (one in posterior-lateral and one in anterior position), and he also had elevated serum metal-ion levels ($>7 \mu\text{g/L}$) [8], but no symptoms. In fact, all patients with a pseudotumor were asymptomatic and revealed similar outcomes in terms of OHS ($p=0.29$), HHS ($p=0.26$) and SF-36 in both mental and physical scores ($p>0.18$). The average levels of chromium and cobalt were much higher in joint fluid than in serum (Table 2). Besides the eight patients with pseudotumors, another 14 patients had a fluid-filled trochanteric bursa, whereas four experienced pain related to the trochanteric bursa.

Metal allergy and atopic dermatitis

Patch test

Three (7.5 %) positive patch test reactions indicating metal allergy were identified in 40 patients although many irritant

reactions were observed ($n=18$). One male and one female had a reaction to nickel (5 %), and one female had a reaction to iron (2.5 %). None of these three patients had pseudotumors, and Fischer's exact test revealed serum metal-ion levels of chromium ($p=0.81$) and cobalt ($p=0.31$) comparable to the levels seen in patients without a positive patch test reaction.

Questionnaire

The results from the questionnaire on previous metal allergies, metal exposures, and history of atopic dermatitis are listed in Table 3.

Serum metal-ion measurements

At the 5–7-year follow-up, serum metal-ion concentrations were obtained from 41 patients. Mean cobalt levels were $2.64 \mu\text{g/L}$ (SD 3.64; range 0.57–21.50) and mean chromium levels were $3.80 \mu\text{g/L}$ (SD 4.83; range 0.57–28.37). Within the patient group, the serum levels of leucocytes, creatinine, GFR, and CRP were normal, except for one patient with congestive heart failure. According to the questionnaires of possible chromium or cobalt exposures, two patients had tattoos, but both had low metal concentrations. Serum metal-ion levels of chromium and cobalt were significantly correlated with cup inclination angles ($r=0.35$, $p=0.01$; and $r=0.33$, $p=0.02$), small femoral-head sizes ($r=-0.30$, $p=0.04$; and $r=-0.32$, $p=0.04$), and were associated with the female gender ($p=0.02$; and $p=0.03$; Table 2). There was a tendency that patients with higher serum metal-ion levels of chromium and cobalt had higher scores of OHS (chromium; $r=0.28$, $p=0.06$; and cobalt; $r=0.28$, $p=0.05$) and physical function in SF-36 (chromium; $r=0.30$, $p=0.05$; and cobalt; $r=0.26$, $p=0.10$). Sub-scores of physical function of SF-36 were significantly higher in patients with elevated serum metal-ion levels ($>7 \mu\text{g/L}$) [8] than in patients with serum metal-ion levels below the recommended level (Fig. 3).

Radiographs, clinical outcome of hip function, and general health

At the 5–7-year follow-up, we found well positioned and well osteointegrated components in all hips ($n=49$), a mean cup inclination of 43° (SD 6; range 33 – 61°), a mean cup anteversion of 25° (SD 6; range 14 – 37°), and a mean femoral head-size of 50 mm (SD 4; range 42–58 mm). Comparison of the postoperative and the 5-year conventional radiographs revealed in total three radiolucent lines (RLL) and two small osteolyses in the DeLee Zones I and II around the cup. There were no RLL or osteolyses around the stem. The clinical outcome satisfaction scores of hip function was mean 43 (SD 9; range 8–48) for the OHS and mean 89 (SD 15; range 12–96) for the HHS.

Table 1 Summary of findings from ultrasonography in those patients with pseudotumors

Patient	Age	Sex	Dimensions (mm) ^a	Location	Appearance	Joint-fluid chromium (ug/L)	Joint-fluid cobalt (ug/L)	Serum chromium (ug/L)	Serum cobalt (ug/L)	Infection	Capsule- stem distance (mm)
1	68	Male	16×15× 20	Posterior/lateral	Cystic	61.21	304.34	1.32	1.74	No	10
2	65	Male	40×35× 110	Anterior	Cystic+solid	2576.29	930.27	10.96	10.34	No	8.6
			25×15× 35	Posterior/lateral	Cystic	2781.63	578.48	10.96	10.34	No	8.6
3	52	Male	15×30× 7.5	Anterior	Cystic	54.75	989.77	2.66	3.68	No	15.3
4	60	Male	2×2× 3	Posterior/lateral	Cystic	145.09	58.18	1.91	1.14	No	5.5
5	47	Male	1×2× 2.5	Posterior/lateral	Solid	–	–	1.64	0.89	–	10.5
6	50	Male	2×3× 2	Posterior/lateral	Solid	–	–	1.68	0.85	–	3
7	62	Female	11×20× 9	Posterior/lateral	Solid	–	–	13.08	8.05	–	4.9
8	50	Male	5×4× 2	Posterior/lateral	Solid	–	–	1.176	0.59	–	7

^a Dimensions refer to the maximum width, height, and depth as measured by ultrasound

Discussion

The aim of this 5–7-year follow-up study was to perform US examination in a consecutive series of large-head MoM THA and to investigate the relationship between pseudotumor formation, metal serum metal-ion levels, metal allergy, and atopic dermatitis. Furthermore, we wanted to assess patients' self-reported hip function and health-related quality of life. We found a pseudotumor incidence of 19.5 %, but no statistically significant association between pseudotumor incidence and serum metal-ion levels, metal allergy, atopic dermatitis or functional outcome.

US scans

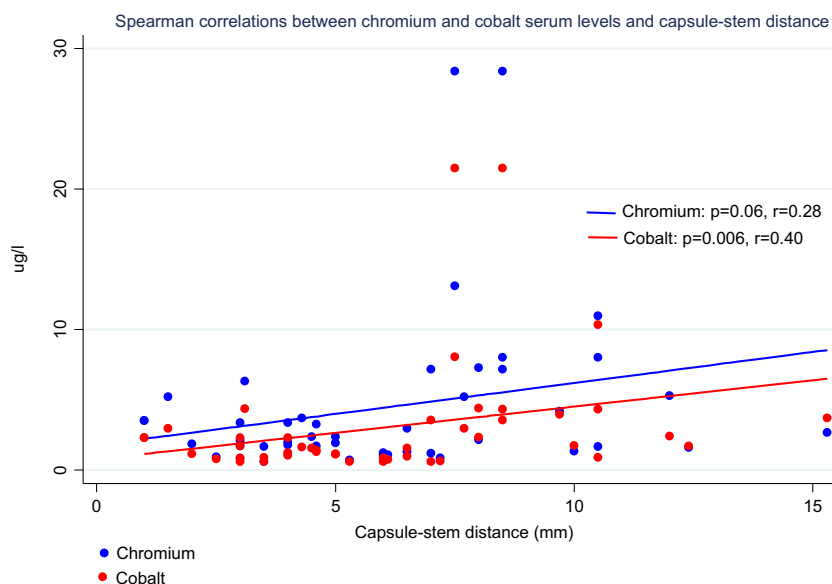
In 39 patients with 46 MoM THA, we found a total of nine (19.5 %) pseudotumors. One patient had two separate pseudotumors in one hip joint. This is a high, but not entirely unexpected level in asymptomatic patients. In a consecutive US study of 88 MoM hip resurfacing arthroplasties (RHA) and large-head MoM THA, Nishii et al. [37] reported an abnormal pattern (defined as joint expansion and cystic and solid masses) in 21.5 % of the hip joints at mean 6 years of follow-up. Furthermore, they reported that the frequency of clinical symptoms was significantly higher in patients with an

Table 2 Results from questionnaires, radiographic data and ultrasonography data and their correlations to serum ion concentrations of chromium and cobalt

Independent variable	Scores; mean (SD) (range)	Serum cobalt; <i>p</i> (<i>r</i>)	Serum chromium; <i>p</i> (<i>r</i>)
Questionnaires			
OHS score (0–48), <i>n</i> =49 hips	42.84 (9.04) (8–48)	0.05 (0.28) ^a	0.06 (0.27) ^a
HHS score (0–100), <i>n</i> =49 hips	88.60 (14.85) (12–96)	0.61 (0.07) ^a	0.24 (0.17) ^a
SF-36 Physical score (0–100), <i>n</i> =41 pt.	47.67 (11.66) (20.63–59.86)	0.10 (0.26) ^a	0.05 (0.30) ^a
SF-36 Mental score (0–100), <i>n</i> =41 pt.	56.14 (10.90) (20.19–74.97)	0.62 (0.08) ^a	0.68 (0.07) ^a
Radiographic data			
Acetabulum cup inclination (°), <i>n</i> =49 hips	43.48 (6.07) (33.05–61.25)	0.02 (0.33) ^a	0.01 (0.35) ^a
Acetabulum cup anteversion (°), <i>n</i> =49 hips	25.23 (6.28) (13.55–37.35)	0.56 (–0.08) ^a	0.94 (–0.01) ^a
Femoral head size	55 (3.85) (48–64)	0.04 (–0.30) ^a	0.02 (–0.32) ^a
Ion measurements			
Serum chromium (ug/L), <i>n</i> =41 pt.	2.64 (3.64) (0.57–21.50)	<0.001 (0.93) ^a	–
Serum cobalt (ug/L), <i>n</i> =41 pt.	3.80 (4.83) (0.57–28.37)	–	<0.001 (0.93) ^a
Joint-fluid chromium (ug/L), <i>n</i> =5 aspirations	1123.79 (1421.97) (54.75–2781.63)	0.80 (0.20) ^a	0.60 (0.40) ^a
Joint-fluid cobalt (ug/L), <i>n</i> =5 aspirations	572.21 (339.55) (58.18–989.77)	0.20 (0.80) ^a	0.40 (0.60) ^a
Ultrasonography data			
Capsule-stem distance, <i>n</i> =49 hips	6.15 (3.23) (1–15.3)	0.006 (0.40) ^a	0.06 (0.28) ^a

^a Spearman correlation analysis

Fig. 2 Spearman correlations between serum metal-ion levels of chromium and cobalt and the capsule-stem distance



abnormal pattern than in patients with a normal hip joint [37]. Also, a recently published study of the ASR MoM device by Hailer et al. [24] reported a significant difference in serum metal-ion levels of chromium and cobalt between patients with and without pseudotumors at 2 years of follow-up [24]. These findings differ from our results where patients with pseudotumors had serum metal-ion concentrations and scores of hip function similar to those of patients without a pseudotumor.

Recently published literature has described that asymptomatic or “silent” pseudotumors is a frequent occurrence in patients with MoM hip articulations [12, 13, 15, 38, 39], but information regarding the M2a-Magnum articulation is sparse. A recent paper reporting on the adverse effects of the M2a-Magnum articulation [11] found a pseudotumor incidence of 39 % at 3.6 years of follow-up, and the study reported that patients with serum metal-ion levels $> 5\mu\text{g/L}$ had a four-fold increased risk of developing a pseudotumor [11]. This is a considerably higher pseudotumor incidence than found in the

present study. However, Bosker et al. [11] used CT scans as screening modality, which means that a direct comparison with their study is difficult. US may have under-reported smaller pseudotumors. We preferred US to MRI or CT scans because it was a more practical method for initial screening of a large number of patients and had the immediate benefit of needle aspiration. MRI and CT scans are arguably more sensitive for small, deep lesions, but the anatomy close to the prosthesis is often obscured by implant-induced metal artefacts. Another important difference between our study and the study of Bosker et al. [11] is the surgical technique; we performed all operations through the posterolateral approach, whereas Bosker et al. performed operations through anterolateral, posterolateral, and minimally invasive approaches [11]. We found that the capsule-stem distance correlated with serum metal-ion levels of cobalt and nearly correlated with the levels of chromium, and that patients with a pseudotumor had a significantly wider capsule-stem distance than patients without a pseudotumor. Two previous US studies on MoM hip

Table 3 Associations between patients with a history of metal hypersensitivity, or patients with atopic dermatitis and patients with a pseudotumor or high serum ion concentrations ($<7\mu\text{g/L}$)

Question from questionnaire	No.	Pseudotumor	Cobalt	Chromium
Have your ears been pierced (yes/no)?	15/41	0.03 ^{b,c}	0.30 ^b	0.42 ^b
Have you ever experienced dermatitis following skin exposure to jewelry, buttons, and watches?	4/41	0.38 ^a	0.91 ^a	1 ^a
Postoperative subsequently redness around the operated hip?	2/41	0.20 ^a	0.72 ^a	1 ^a
Postoperative progress in hypersensitivity?	5/41	0.56 ^a	0.86 ^a	1 ^a
Have you ever experiences dermatitis in the hollow of the knee or the cubital fossa?	4/41	0.53 ^a	0.99 ^a	1 ^a

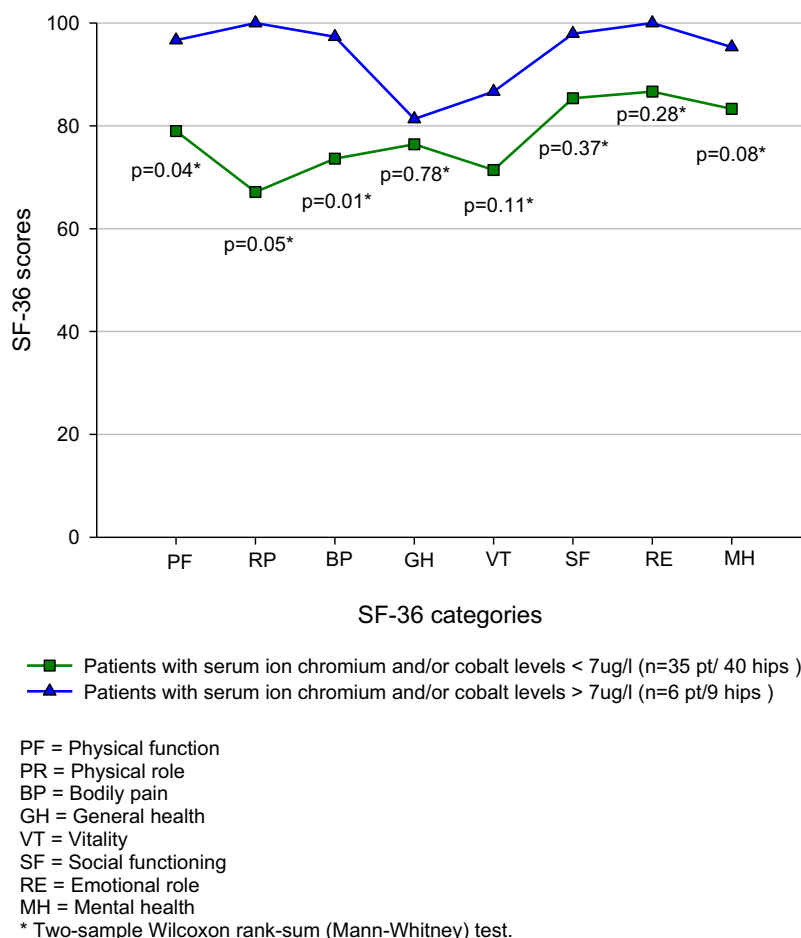
^a Fisher’s exact test

^b Chi-square test

^c No patients with a pseudotumor previously had their ear pierced

Fig. 3 Sub-scores of SF-36 and associations with elevated serum metal-ion levels of chromium and cobalt

Sub-scores of SF-36 and associations to elevated serum ion levels



articulations have described a capsule-stem distance of 4 mm or more to be equal to joint effusion. The authors suggested that a joint effusion could be caused by aseptic synovitis and that it could possibly be a result of metal particle disease [37, 40]. Van Holsbeeck et al. performed US scans in 15 asymptomatic volunteers after THA and compared the findings with the findings in 33 patients who suffered from hip pain and demonstrated radiologic findings of loosening. They found that a capsule-stem distance of 3.2 mm or more indicated an infected or loose THA [41]. Little is known about the clinical importance of the capsule-stem distance and asymptomatic pseudotumors in MoM hip articulations, and this may be a relevant aspect to include in future studies.

Metal allergy and atopic dermatitis

We found three (7.5 %) patients with a positive patch test reaction—2 (5 %) to nickel and one (2.5 %)—to iron. Patients with a positive patch test reaction did not have pseudotumors or higher serum metal-ion levels than patients without a positive patch test reaction. Glyn-Jones et al. [42] reported an 8-

year cumulative revision rate for pseudotumors in MoM RHA of 9 % in females and 0.5 % in males, and suggested that a possible reason could include an increased prevalence of metal allergy in females due to wearing jewelry [42]. We found one female and seven males with a pseudotumor, and it appears that the females in this study were not more likely to exhibit pseudotumors than the males; however, we patch-tested a total of 40 patients of whom only 10 were females. Metal allergy to nickel, cobalt, and chromium is prevalent in the general population, with nickel sensitivity having the highest prevalence [43]. We found no patients with chromium or cobalt allergy, but two patients had nickel allergy. In the Danish population, the prevalence of nickel allergy was estimated to 5.9 % in 2009, with a higher frequency found in females (10 %) and a lower in males (1 %) [44]. These estimates are very comparable to the prevalence found in this study where 1/10 (10 %) females and 1/30 (3.3 %) males had nickel allergy. We therefore find it reasonable to believe that patients were not sensitized to metal due to their large-head MoM THA at 5–7 years after surgery. However, as patients were not examined with patch tests preoperatively, we

cannot evaluate if an actual increase in the prevalence of metal allergy had happened after surgery, but we judge it to be unlikely. Four patients (9.7 %) had atopic dermatitis, but none of them had pseudotumors, and their serum metal-ion levels were similar to those of patients without atopic dermatitis. Even though it was recently shown that patients with atopic dermatitis were more likely to develop contact allergy to metal allergens [17] and, furthermore, that patients with symptomatic knee or hip articulations had higher rates of atopic dermatitis than asymptomatic patients [45], we found no association between atopic dermatitis and adverse effects in large-head MoM THA.

We observed 18 patients with irritant reactions; these patients had more pseudotumors (6/8) and higher serum metal-ion levels than patients without an irritant reaction; however, the difference was not significant ($p>0.12$). Interleukin-1 (IL-1) is known to induce inflammatory responses as a reaction to metal in both periprosthetic and dermal tissue, and IL-1b release was recently shown to be significantly higher among patients with titanium dental implants [46]. The relationship between MoM hip failure and IL-1b may be a goal for future research. However, at present, we have no insight into the association with skin irritation.

Serum metal-ion measurements

In agreement with previous studies, we found that serum metal-ion concentrations were significantly correlated with steeper cup inclination angles, smaller femoral heads, and female gender [47–49]. We found a trend that patients with higher serum metal-ion concentrations had higher OHS scores of hip function and higher SF-36 scores of physical function. This may be explained by younger patients having an active lifestyle as the higher activity levels generate a larger production of metal wear debris, consequently leading to higher serum metal-ion concentrations [50, 51].

We had 13 patients with bilateral MoM articulations of different types, which might have biased the correlations and associations with serum metal-ion concentrations found in the present study. Also, the study is limited by the small number of participants, which makes the statistics more sensitive to coincidences and outliers. However, our results are similar and supportive to those found in previous studies of MoM articulations and therefore we trust our results to be valid.

In conclusion, Pseudotumors were found in eight patients, but they were asymptomatic and their serum metal-ion levels were similar to those found in patients without a pseudotumor. We did not identify an association between patients with pseudotumors, high serum metal-ion levels, metal allergy or atopic dermatitis. However, the capsule-stem distance was significantly larger in patients with a pseudotumor than in patients without a pseudotumor. Serum metal-ion levels of chromium and cobalt were correlated with steeper cup

inclination angles, smaller femoral head sizes, and female gender. There was a tendency that patients with high serum metal-ion levels had wider capsule-stem distances, higher scores of OHS, and higher SF-36 physical component scores.

The pathogenesis and the actual prevalence of asymptomatic patients with low serum metal-ion levels who develop pseudotumors remain insufficiently explored. Whether pseudotumors occur in metal-on-polyethylene, ceramic-on-polyethylene, or ceramic-on-ceramic articulations remains to be determined, and this issue could be a topic for further investigation. We advise further exploration into the potential mechanisms involved in the pathogenesis of pseudotumors.

MoM metal-metal, THA total hip arthroplasty, RHA hip resurfacing arthroplasty, US ultrasonography, MRI magnetic resonance imaging, MARS metal artifact reduction sequence, CT computed tomography, ALVALs aseptic lymphocytic vasculitis-associated lesions, ARMD adverse reaction to metal debris, OHS Oxford Hip Score, HHS Harris Hip Score, SF-36 Short Form Health Survey, SD standard deviation.

Acknowledgements We thank Lone Løvgren, Rikke Mørup, and Inger Krog-Mikkelsen for their help with arranging the 5–7-year follow-up.

Authors' contributions All authors made substantive intellectual contributions to this study to qualify as authors. MHH, KS, MS, IM, JSS, LB, and JPT were involved in the study hypothesis and follow-up examinations. MHH performed the data analyses and wrote the initial manuscript. MS, IM, KS, JSS, LB, and JPT helped revise it. All authors read and approved the final manuscript.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

References

1. Bolland BJ, Culliford DJ, Langton DJ, Millington JP, Arden NK, Latham JM. High failure rates with a large-diameter hybrid metal-on-metal total hip replacement: clinical, radiological and retrieval analysis. *J Bone Joint Surg Br.* 2011;93(5):608–15.
2. Gill IP, Webb J, Sloan K, Beaver RJ. Corrosion at the neck-stem junction as a cause of metal ion release and pseudotumour formation. *J Bone Joint Surg Br.* 2012;94(7):895–900.
3. Malviya A, Ramaskandhan JR, Bowman R, Hashmi M, Holland JP, Kometa S, et al. What advantage is there to be gained using large modular metal-on-metal bearings in routine primary hip replacement? A preliminary report of a prospective randomised controlled trial. *J Bone Joint Surg Br.* 2011;93(12):1602–9.
4. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90(7):847–51.
5. Goodman SB. Wear particles, periprosthetic osteolysis and the immune system. *Biomaterials.* 2007;28(34):5044–8.
6. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, et al. Metal-on-metal bearings and hypersensitivity in patients

- with artificial hip joints: a clinical and histomorphological study. *J Bone Joint Surg Am.* 2005;87(1):28–36.
7. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: a consequence of excess wear. *J Bone Joint Surg Br.* 2010;92(1):38–46.
 8. Medicines and Healthcare products Regulatory Agency. Medical device alert: all metal-on-metal (MoM) hip replacements. 2010 (MDA/2010/03). London: MHPRA. 2010 [cited 2014 April 03]. Available from: <http://www.mhra.gov.uk/home/groups/dts-bs/documents/medicaldevicealert/con079162.pdf>
 9. Lombardi Jr AV, Barrack RL, Berend KR, Cuckler JM, Jacobs JJ, Mont MA, et al. The Hip Society: algorithmic approach to diagnosis and management of metal-on-metal arthroplasty. *J Bone Joint Surg Br.* 2012;94(11 Suppl A):14–8.
 10. Sofka CM, Potter HG, Adler RS, Pavlov H. Musculoskeletal imaging update: current applications of advanced imaging techniques to evaluate the early and long-term complications of patients with orthopedic implants. *HSS J.* 2006;2(1):73–7.
 11. Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC. High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. *J Bone Joint Surg Br.* 2012;94(6):755–61.
 12. Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, et al. Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. *J Bone Joint Surg Am.* 2012;94(4):317–25.
 13. Chang EY, McAnally JL, Van Horne JR, Statum S, Wolfson T, Gamst A, et al. Metal-on-metal total hip arthroplasty: do symptoms correlate with MR imaging findings? *Radiology.* 2012;265(3):848–57.
 14. Donell ST, Darrah C, Nolan JF, Wimhurst J, Toms A, Barker TH, et al. Early failure of the Ultima metal-on-metal total hip replacement in the presence of normal plain radiographs. *J Bone Joint Surg Br.* 2010;92(11):1501–8.
 15. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop Relat Res.* 2012;470(7):1895–906.
 16. Thomas P, Braathen LR, Dorig M, Aubock J, Nestle F, Werfel T, et al. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy.* 2009;64(8):1157–65.
 17. Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. *J Am Acad Dermatol.* 2013;69(2):232–7.
 18. Biomet. M²a-Magnum large metal articulation: design rationale. Warsaw, IN: Biomet; 2009 [cited 2014 April 07]. Available from: <http://www.biomet.com/campaign/trueAlternativeBearings/BOI03400MagnumDesignRationale.pdf>
 19. Murray DW, Fitzpatrick R, Rogers K, Pandit H, Beard DJ, Carr AJ, et al. The use of the Oxford hip and knee scores. *J Bone Joint Surg Br.* 2007;89(8):1010–4.
 20. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty—an end-result study using a new method of result evaluation. *J Bone Joint Surg Am.* 1969;51(4):737–55.
 21. Björner JB, Thunedborg K, Kristensen TS, Modvig J, Bech P. The Danish SF-36 Health Survey: translation and preliminary validity studies. *J Clin Epidemiol.* 1998;51(11):991–9.
 22. Craig JG. Ultrasound of the postoperative hip. *Semin Musculoskelet Radiol.* 2013;17(1):49–55.
 23. Long SS, Surrey D, Nazarian LN. Common sonographic findings in the painful hip after hip arthroplasty. *J Ultrasound Med.* 2012;31(2):301–12.
 24. Hailer NP, Bengtsson M, Lundberg C, Milbrink J. High metal ion levels after use of the ASR device correlate with development of pseudotumors and T cell activation. *Clin Orthop Relat Res.* 2014;472(3):953–61.
 25. Cervini P, Hesley GK, Thompson RL, Sampathkumar P, Knudsen JM. Incidence of infectious complications after an ultrasound-guided intervention. *AJR Am J Roentgenol.* 2010;195(4):846–50.
 26. Dramis A, Aldlyami E, Grimer RJ, Dunlop DJ, O’Connell N, Elliott T. What is the significance of a positive *Propionibacterium acnes* culture around a joint replacement? *Int Orthop.* 2009;33(3):829–33.
 27. Becton Dickinson. Franklin Lakes, NJ: Becton Dickinson. 2013 [cited 2014 May 01]. <http://www.bd.com/resource.aspx?IDX=10155>
 28. Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: results from two cross-sectional studies. *Contact Dermatitis.* 2009;61(6):342–8.
 29. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am.* 2001;83-A(3):428–36.
 30. MacDonald SJ, Brodner W, Jacobs JJ. A consensus paper on metal ions in metal-on-metal hip arthroplasties. *J Arthroplasty.* 2004;19(8 Suppl 3):12–6.
 31. Penny JO, Overgaard S. Serum chromium levels sampled with steel needle versus plastic IV cannula: does method matter? *J Biomed Mater Res B Appl Biomater.* 2010;92(1):1–4.
 32. Papageorgiou I, Yin Z, Ladon D, Baird D, Lewis AC, Sood A, et al. Genotoxic effects of particles of surgical cobalt chrome alloy on human cells of different age in vitro. *Mutat Res.* 2007;619(1–2):45–58.
 33. DeLee JG, Charnley J. Radiological demarcation of cemented sockets in total hip replacement. *Clin Orthop Relat Res.* 1976;121:20–32.
 34. Gruen TA, McNeice GM, Amstutz HC. “Modes of failure” of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin Orthop Relat Res.* 1979;141:17–27.
 35. Brooker AF, Bowerman JW, Robinson RA, Riley Jr LH. Ectopic ossification following total hip replacement: incidence and a method of classification. *J Bone Joint Surg Am.* 1973;55(8):1629–32.
 36. Altman DG. Practical statistics for medical research. London: Chapman and Hall, 2009. ISBN 9780412276309
 37. Nishii T, Sakai T, Takao M, Yoshikawa H, Sugano N. Ultrasound screening of periarticular soft tissue abnormality around metal-on-metal bearings. *J Arthroplasty.* 2012;27(6):895–900.
 38. Williams DH, Greidanus NV, Masri BA, Duncan CP, Garbus DS. Prevalence of pseudotumor in asymptomatic patients after metal-on-metal hip arthroplasty. *J Bone Joint Surg Am.* 2011;93(23):2164–71.
 39. Wynn-Jones H, Macnair R, Wimhurst J, Chirodian N, Derbyshire B, Toms A, et al. Silent soft tissue pathology is common with a modern metal-on-metal hip arthroplasty. *Acta Orthop.* 2011;82(3):301–7.
 40. Siddiqui IA, Sabah SA, Satchithananda K, Lim AK, Henckel J, Skinner JA, et al. Cross-sectional imaging of the metal-on-metal hip prosthesis: the London ultrasound protocol. *Clin Radiol.* 2013;68(8):e472–8.
 41. van Holsbeeck MT et al. Detection of infection in loosened hip prostheses: efficacy of sonography. *AJR Am J Roentgenol.* 1994;163:381–4.
 42. Glyn-Jones S, Pandit H, Kwon YM, Doll H, Gill HS, Murray DW. Risk factors for inflammatory pseudotumour formation following hip resurfacing. *J Bone Joint Surg Br.* 2009;91(12):1566–74.
 43. Thyssen JP, Linneberg A, Menne T, Johansen JD. The epidemiology of contact allergy in the general population: prevalence and main findings. *Contact Dermatitis.* 2007;57(5):287–99.

44. Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. *Br J Dermatol*. 2009;161(5):1124–9.
45. Thomas P, Stauner K, Schraml A, Mahler V, Banke IJ, Gollwitzer H, et al. Characteristics of 200 patients with suspected implant allergy compared to 100 symptom-free arthroplasty patients. *Orthopade*. 2013;42(8):607–13.
46. Jacobi-Gresser E, Huesker K, Schutt S. Genetic and immunological markers predict titanium implant failure: a retrospective study. *Int J Oral Maxillofac Surg*. 2013;42(4):537–43.
47. Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AV. The effect of component size and orientation on the concentrations of metal ions after resurfacing arthroplasty of the hip. *J Bone Joint Surg Br*. 2008;90(9):1143–51.
48. de Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De SK. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br*. 2008;90(10):1291–7.
49. Hart AJ, Buddhdev P, Winship P, Faria N, Powell JJ, Skinner JA. Cup inclination angle of greater than 50 degrees increases whole blood concentrations of cobalt and chromium ions after metal-on-metal hip resurfacing. *Hip Int*. 2008;18(3):212–9.
50. De HR, Campbell P, Reid S, Skipor AK, De SK. Metal ion levels in a triathlete with a metal-on-metal resurfacing arthroplasty of the hip. *J Bone Joint Surg Br*. 2007;89(4):538–41.
51. Pattyn CA, Lauwagie SN, Verdonk RC. Whole blood metal ion concentrations in correlation with activity level in three different metal-on-metal bearings. *J Arthroplasty*. 2011;26(1):58–64.