Metal-on-Metal Hip Arthroplasty

Physical Activity Monitoring, Outcomes and Systemic Toxicity

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Chapter I

General Introduction

Je gaat het pas zien als je het door hebt

(Johan Cruijff)

1. Introduction

Hip osteoarthritis (OA) is one of the most prevalent and disabling conditions affecting the elderly, as it often includes the loss of autonomy [1, 2]. The lifetime risk of complaints caused by OA is approximately 25% in people who live to an age of 85 years. Hip OA is a disease of the joint that disrupts the normal homeostatic balance between joint tissue synthesis and degradation, which means that normal biomechanical stresses become disruptive. Risk factors for OA can be divided into joint-related factors (e.g. joint morphology, muscular function, joint shape) and person-related factors (e.g. age, sex, weight, genetics, ethnicity, occupation, diet) [1]. Usually, management of hip OA begins after the onset of symptoms. At this point, there is often already significant joint damage. Non-surgical management consists of weight loss and a dietary program, exercise with physiotherapy and pharmacological management. There is no truly curative treatment [2]. In case of daily invalidating complaints, a surgical intervention might be chosen.

Total hip arthroplasty (THA) or total hip replacement (THR) is considered to be one of the most successful surgical procedures and was appointed 'the surgical procedure of the 20th century' [3, 4]. It is considered the best treatment option for patients who are highly invalidated by (end-stage) OA, which may cause pain, joint stiffness, functional disability and limitations in their activity [5]. Other indications for THA are acute femoral fractures, osteonecrosis, late post-traumatic OA, rheumatoid arthritis, post-Perthes disease and tumours [6]. Each year, 1 million THA procedures are performed worldwide [7]. Based on the Dutch Arthroplasty Register (LROI), which covers 99% of all THAs in the Netherlands, 33.248 THA procedures were performed in the Netherlands in 2019. The patients' mean age was 69.1 ± 10.4 years, 64% were female and in 87%, the indication for surgery was OA. Since the introduction of the LROI, the number of procedures has increased yearly [6]. THA is increasingly offered to younger OA patients, and it is expected that by 2030, half of all arthroplasty procedures will be performed on patients younger than 65 [8]. Patients receiving THA at any age tend to have high demands on functional outcomes, which increases the need for durability of the different prostheses.

2. Development of total hip arthroplasty

The history of hip arthroplasty dates back to 1821, when excision arthroplasty was performed by Antony White (1782 – 1849). With this intervention, pain was reduced and mobility maintained, but a main disadvantage was instability of the hip joint

[9, 10]. The procedure became popular due to the lack of other options. In the subsequent years, interpositional arthroplasty was performed using skin, fascia, muscle, pig bladder, celluloid, silver plates, rubber struts, magnesium, zinc, glass, Pyrex, decalcified bone and wax [11-13]. These interventions were all painful and subsequently failed [9, 10].

2.1. Design

The first surgeon reported to perform a THA was Themistocles Glück (1853 – 1942). In 1891, he replaced a tuberculous hip joint with an ivory ball and socket, which were fixed with nickel-plated screws. The replacements were successful in the short term, but failed due to chronic infection [9, 10]. Marius Smith-Petersen (1886 – 1953) was the first to perform mould arthroplasty, which he explained as the principle of guiding the repair of nature for the purpose of recreating a destroyed or damaged structure. He created the first mould arthroplasty out of glass, which he implanted for the first time in 1923. It consisted of a hollow hemisphere fitting over the femoral head. The moulds were removed after 15 to 25 months, when the joint surfaces were smooth, glistening, firm and congruous. However, the glass moulds had a high risk of breaking. On the advice of his dentist, Smith-Petersen constructed a mould with vitallium, a metallic alloy consisting of cobalt, chromium and molybdenum. Smith-Petersen performed the first vitallium mould arthroplasty in 1938, followed by a total of 500 arthroplasties, with acceptable and predictable results. A revision was performed in 53 cases [14].

In 1938, Philip Wiles (1899 – 1966) was the first to perform a hip arthroplasty using a metal acetabular component and a metal head for articulation (figure 1). He used stainless steel components, and the replacement was attached to the outside of the bone with a metal plate and screws. The results were not satisfactory due to accelerated wear and thus early failures [15]. The phenomenon 'wear' is defined as a progressive loss of material (debris) due to the friction between moving surfaces [16].

In 1948, Robert Judet (1901 – 1980) and his brother Jean Judet (1905 – 1995) used a prosthesis made of polymethyl-methacrylate (PMMA)(Figure 2) [18]. This material was already used by ear-nose-throat doctors. The prosthesis was shaped like a mushroom, consisting of a rounded head and a long stem. The procedure was called 'resection-reconstruction' or 'prosthetic replacement of the femoral head'. The femoral head was thought to be the generator of pain in OA, and thus replacement was expected to lead to a decrease in pain. In the first cases, the stem broke, and hence the stem was reinforced. The brothers reported that seven out of ten patients

had no or a negligible amount of pain in the postoperative phase. Unfortunately, the prosthesis was very susceptible to wear [16]. Unsatisfactory results were shown by the Judet brothers in 1952 [19]. In the years after, several surgeons attempted to improve the Judet prosthesis, which resulted in the Thompson prosthesis, the Jaenichen-Collison prosthesis and the Fitzgerald prosthesis, all of which were hemiarthroplasties, i.e., replacements of the femoral head only, leaving the acetabular site untouched [20-22]. George McKee (1906-1991) and John Watson-Farrar (1926-1999) reported that replacement of the femoral head only tackles half of the problem if degenerative changes are present in the acetabulum [23].

Figure 1. The first MoM THA by Philip Wiles (1938)[15].
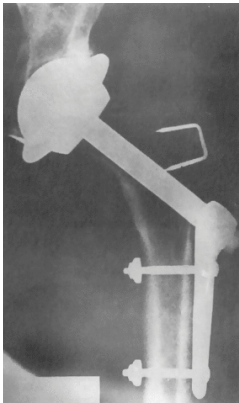
Figure 2. The standard Judet prosthesis and a modification with four X-ray wire markers [17].
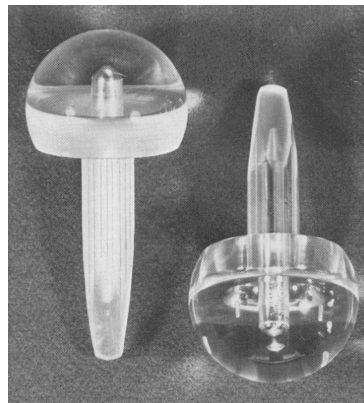
Both mould arthroplasty and the Judet prosthesis can be seen as precursors of hip resurfacing arthroplasty (HRA). This is a procedure in which a hollow, mushroom-shaped cap is placed over the head of the femur and a matching cup is placed in the acetabulum. In the late 1950s, Charnley (1911-1982) used a Teflon double cup, and Townley (1916-2006) used a polyurethane to anchor a metal cup to the femoral head and resurface the acetabulum (1960). Muller (1918-2009) used a prosthesis with both components made of cobalt-chrome (1968), and Freeman (1931-2017) used a metal-on-polyethylene (MoP) combination in the early 1970s. All these approaches showed early failures, which were partly due to polyethylene debris and the ensuing development of osteolysis, which resulted in prosthetic loosening, and to a lack of surgical experience [24-26].

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The failures of metal-on-metal (MoM) bearings were due to local effects of metal particles, which were noted during revision surgery [3]. These failures were explained by mechanical and biological facts (aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL)). When a MoM bearing is placed on a titanium stem, the cam effect generates a 'titanosis'. This is a type of metallosis that is not specific to MoM bearings [27]. A solution was found in the use of larger diameter femoral heads, which would result in a better lubrication and would increase stability and mobility. This solution also meant a return to HRA, a procedure that has various theoretical advantages over conventional stemmed THA: low volumetric wear, a femoral head with large physiological diameter offering stability, near-natural joint kinematics, an increased range of motion compared to small-diameter THA, and preservation of the femoral bone, which allows an easy revision if needed [28].

2.2. Fixation

The modern era of THA began with the ideas of Sir John Charnley (1911 –1982). His low-friction arthroplasty consisted of three parts, which in principle were identical to the prostheses used today: a polyethylene acetabular component and a metal femoral stem, both fixated to the bone by means of acrylic bone cement. The early results of ultrahigh-molecular-weight polyethylene (UHMWPE) compared to Teflon were very impressive, and the durability improved. At this point, the focus changed to understanding fatal pulmonary embolism (2%), high infection rates (±10%) and cement fixation failures [29]. Periprosthetic osteolysis was seen in longer follow-up of THA, which was an unexpected and initially unrecognized complication leading to failure. Research showed that this periprosthetic osteolysis was due to a macrophage-induced response to polyethylene wear particles. Cement was considered the cause of poor outcomes ('cement disease'), while in many cases, the main causes actually were the implant design and the cementing technique [30].

Thinking that 'cement disease' was the main cause of failure of cemented THA, surgeons were motivated to search for uncemented options. However, the smooth surfaces of the uncemented implants developed in the 1970s could not achieve a strong adherence to bone. Coating materials that allowed bone ingrowth and ongrowth became available in the 1980s and gained favour for the uncemented hip arthroplasty [30]. Osseointegration was described as "the attachment of lammelar bone to implants without intervening fibrous tissue"[31]. Initial stability and osseous contact were necessary to hold the prosthesis steady while bone could form and adhere to the porous prosthesis surface. Where micromotion was very low, bone would form,which demonstrated the importance of initial stability [32]. Prevention

of stress shielding, i.e., the decreased loading of the proximal femoral bone due to a stiffer implant made of metal, was obtained by ensuring that the implant has a low Young's modulus, which is the measure of the rigidity of an object. Stress shielding occurs because of the difference in stiffness between implantand bone, which might result in a decreased loading of bone and therefore in increased bone resorption (Wolff's law) and finally in an increased rate of aseptic loosening [33]. However, implant survival is also determined by the elasticity modulus, because a low Young's modulus indicates less rigidity and results in more micromotion, which is negative for the bone-implant interface [34]. In the manufacturing of hip implants, a compromise is needed, since a high Young modulus is required to prevent aseptic loosening, whereas a low Young modulus is required to prevent stress shielding [35]. More stress shielding is observed in uncemented hip arthroplasty, because the need for a larger diameter results in a stiffer stem, creating more stress shielding than in cemented hip arthroplasty. Because of the optimal Young's modulus of bonecement and the reduced diameter of a cemented stem, cement fixation of the femoral implant in general induces less stress shielding than an uncemented fixation.

Currently, uncemented fixation of THA is the most frequently used fixation type in THA. In 2019, uncemented fixation was used in 68% of primary THA procedures in the Netherlands [6]. However, cementing techniques have been improved in the past few decades; the current fourth generation of cementation consists of a canal plug, serial high-pressure pulse lavage, retrograde filling of the femoral canal and proximal pressurization with later insertion of an implant into viscous cement. This is considered the gold standard in modern cemented arthroplasty [32].

2.3. Bearing

The normal joint loads and motions must be transmitted by the bearing surfaces of a hip prosthesis. The bearing or bearing surface is the area of contact between two objects [36]. Selecting the best material for the bearing has been an issue since the beginning of THA. Glück used an ivory ball and socket (1891), whereas Wiles used a metal acetabular component and a metal head (1938) [9, 10, 15]. Since the 1950s, MoM THA was used by George McKee and John Watson-Farrar. They used a ball and socket type replacement consisting of a chrome-cobalt alloy. A modified Thompson stem was used, in combination with a cup that was screwed in the acetabular roof. After Sir John Charnley described the use of methylmethacrylate to anchor a Thompson prosthesis within the femoral shaft, McKee-Farrar designed a new acetabular prosthesis, which was used regularly [23]. However, later research showed high revision rates. The MoM method became unpopular due to the local

effects of metal particles which were noted during revision surgery [3]. The McKee-Farrar and Ring models were abandoned in the 1970s, in favour of Charnley's ideas [9]. Charnley used small femoral heads, based on the theory that this smaller surface area would reduce wear based on friction. He understood that low friction wear was more important than low pressure wear, so a smaller head was used (Low Friction Arthroplasty Concept) [3]. The early results of Charnley's UHMWPE were very impressive and the durability improved [29].

The implant failure of THA based on polyethylene wear known as 'polyethylene disease' led to renewed interest in hard bearings such as MoM and ceramic-on-ceramic (CoC). A CoC-bearing has a high resistance to wear due to its hardness and wettability. It was shown that wear rates were a 50-fold lower than those of UHMWPE [37]. Nevertheless, the bearing was never widely used due to the risk of fracture, problems in achieving a durable fixation between bone and ceramic implants and the higher costs. Also, ceramic liners are sensitive to implant positioning. Squeaking is a well-known negative side effect of CoC-bearings, although it does not influence hip function, nor is loosening or osteolysis more frequent in 'squeaking' hips [37].

When Bernhard Georg Weber (1927–2002) observed that certain MoM prostheses functioned well at long-term follow-up, he hypothesized that failure was due to unsuitability of the bearing materials used, the design of the implant, or technical errors. Weber and his industrial partner manufactured the Metasul bearing [27, 38]. Since 1992, Weber has used uncemented components (Metasul bearing in a Zweymüller cup) and proved reliable and satisfactory long-term results.

Derek McMinn (1953-, United Kingdom), Michael Wagner (1957-, Germany) and Harlan Amstutz (1931-, USA) were the first to start implanting HRA with a MoM articulation [39-41]. In-vivo wear rates in these 'second generation' MoM bearings were almost 100 times lower than in MoP bearings, and the small particles were less likely to induce the macrophage-induced response observed in MoP bearings leading to osteolysis [42,43]. In the early 2000s, the worldwide popularity of HRA increased because of excellent early short-term results [44]. An estimated 1 to 1.5 million patients received a MoM hip arthroplasty, either HRA or large-head MoM (LHMoM) THA [45,46]. The use of LHMoM THA was popularized in parallel with HRA. In 2002, Korovessis et al. reported that there "was no evidence that MoM articulation gives rise to new problems or complications" [47]. The future would prove, however, how mistaken they were.

Figure 3. **Example of HRA and LHMoM THA system (Conserve® Plus; Wright Medical Technology, Memphis, TN, USA)[48].**

2.4. Metal-on-metal issues

Concerns have been voiced since the beginning of MoM arthroplasty. Local tissue reactions were already described in 1975, and in 1994, studies found dissemination of cobalt and chromium ions into the lymphatic system, liver, and spleen. In 1998, cobalt and chromium ions were shown to be toxic to monocytes in culture [45]. The first results published by McMinn in 2003 concerning the Birmingham Hip Replacement (BHR) started the trend for larger heads in hip arthroplasty [45]. Since 2004, concerns increased. Multiple studies including national registry data showed high failure rates as neither HRA nor LHMoM THA achieved the 10-year survival rate threshold of 95% set in 2000 by the National Institute for Health and Care Excellence (NICE) [49,50]. In 2005, an internal memo of DePuy showed that manufacturers were aware of the potential genotoxicity, but stated that 'the ultimate test is the long term human experience'. A year after, dr.Schmalzreid, one of DePuy's prosthesis designers

and an orthopaedic surgeon, wrote a paper to counter emerging concerns about MoM hip arthroplasty [45].

On 7 September 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) recalled the Articular Surface Placement (ASR) (DePuy Orthopaedics, Warsaw, Indiana, USA) hip prosthesis. Consequently, this implant was withdrawn by the manufacturer [51]. Failure rates of 25% to almost 50% were shown for the ASR HRA and LHMoM, respectively [52]. It was shown that after implantation, all patients with a MoM hip prosthesis had raised metal ion concentrations of cobalt and chromium in body fluids (blood, serum, plasma, urine) [53]. Blood or serum metal ion concentrations are used as a surrogate marker of in-vivo wear [54]. These concentrations might be influenced by a variety of parameters, which can be divided into patient factors (female sex, age at surgery (young), time since implantation), implant factors (bilateral, small femoral HRA components, design, type of implant (HRA/LHMoM)) and surgical factors (acetabular component malposition, reduced contact patch to rim distance)[55]. There was a concern that increased cobalt and chromium ion concentrations increased the risk for cancer, but this was proven otherwise in large comparative studies [56,57]. Nevertheless, in 2012, the NetherlandsOrthopaedicAssociation (NOV) advised against the use of any MoM hip arthroplasty [58,59]. New ideas led to UHMWPE crosslinking plus melting or crosslinking with added antioxidants. These innovations resulted in metal- and ceramic-on-polyethylene as the most frequently used bearings in THA, also in the Netherlands [3, 6, 29].

3. Clinical results and assessment of THA

Outcome measures are used to assess change over time as well as the response to any type of intervention. Outcome after THA can be assessed in multiple ways and based on different judgements: by the clinician, by the patient, by 'a significant other' or by a combination of two or more of those concerned [60]. The main outcomes of THA studied over time were implant position determined via radiographs, common adverse events and serious adverse events (SAEs) (e.g. infection), and survival of prosthesis, whereas clinical improvement and patient experience were thought to be not really relevant at that time [61]. Clinician-administered outcome assessment became more important due to improvements in prosthesis design, operative techniques, perioperative treatments and the prevention of SAEs. These assessments consisted of measures of pain, activity and joint function (e.g. the Harris Hip Score (HHS)) [62].

3.1. Subjective outcome assessment

Clinician-administered tools have shown disagreements between patients and clinicians and were therefore widely criticised [63]. The focus shifted to improving the patients' health-related quality of life, which increased the importance of outcome experiences and of the patients' and the clinicians' expectations regarding the outcomes of an intervention. Patient-reported outcome measures (PROMs) are often questionnaires that are completed by the patients themselves and that measure functional status, health-related quality of life, symptoms and symptom burden, personal experience of care, and health-related behaviors, such as anxiety and depression. PROMS can be both generic and disease-specific [64]. Life and health changes continuously and well-being is influenced by many factors, which means that PROM results are subjective by nature and influenced by socioeconomic and psychological factors [60,65,66]. For many PROMs, the main determinant of outcome seems to be pain, because patients experience difficulties in differentiating between pain and functional disability [67,68]. These drawbacks influence the validity of PROMS, especially in the assessment of objectively measurable dimensions of outcome, such as physical function [67,69]. PROM results are highly influenced by a patient's postoperative pain relief, which results in overestimation of the actual short- and long-term changes in physical function [70-73]. While PROMs are commonly used, their outcomes can suffer from their subjective nature, recall bias, ceiling effects, low response and completion rates or transcription errors, as well as from the fact that PROMS are a time-consuming method for outcome assessment [74-77].

3.2. Objective outcome assessment

Rather than by subjective assessments of clinicians or patients, the outcomes of hip arthroplasty should be determined by means of objective measurements. Physical activity (PA) is an outcome measure after hip arthroplasty that can be objectively determined in various ways, for instance by using optical motion capture systems, force platforms, isometric strength testing techniques, electromyography, timed performance-based tests (six minute walk test, timed up-and-go test) or by means of wearable sensor techniques (inertial measurement units (IMU), accelerometers) [78-81]. Activity monitoring with the use of continuous activity monitors (AMs) during activities of daily life (ADL; 'the free-living environment') capturing PA has become possible due to advances in measurement accuracy, monitor size and costs. AMs can measure behavioral aspects of PA (e.g. number of steps) as well as qualitative aspects (e.g. steps per minute). For several studies presented in this thesis, activity monitoring was performed using a 3-axis accelerometer, gyroscope and magnetometer. Patients were monitored for four consecutive days, since a

patient's habitual PA patterns can be representatively characterized by measuring activity for three to four days [82,83]. The raw signal received with this AM was analysed using published algorithms. This approach has been previously described and validated in a semi-free setting and achieved an excellent accuracy (>97%) in determining PA levels in healthy subjects and patients after unilateral hip or knee arthroplasty [84, 85].

4. Aims of this thesis

In MoM hip arthroplasty, the metal surfaces are exposed to wear, which results in the release of metal ions during articulation. An indirect measure of (volumetric) wear is the concentration of metal ions in blood, serum or urine [86-88]. Dr. Schmalzried discovered that "wear is a function of use, not time" in THA with a polyethylene bearing [89]. Little is known about the influence of PA on metal ion concentrations, while in theory the daily habitual PA of patients with a MoM hip arthroplasty should be associated with metal ion concentrations in blood.

HRA was designed for highly active patients because of the various previously mentioned theoretical advantages over conventional stemmed MoP THA [28]. It can be expected that patients who received an HRA would be more physically active after surgery because of these advantages. In current literature, the only evidence available is based on self-reported activity questionnaires [90,91]. As PROMs suffer from their subjective nature, a precise analysis of the effects of PA in patients with HRA and conventional stemmed MoP THA might benefit from objective PA monitoring. In addition, to determine the value of PROMs concerning PA, PROM results should be compared with objectively measured PA.

One of the advantages of HRA is the preservation of the femoral bone, which allows an easy revision if needed. While the outcome of revision of a MoM hip arthroplasty might depend on the reason for revision, current literature on this topic is not clear. However, it is clear that MoM articulation results in local tissue reactions and raised metal ion concentrations locally but also systemically. Systemically raised metal ion concentrations are seen in all patients, with peak concentrations being reached between 9 and 18 months postoperatively. The systemic danger of highly and chronically raised metal ion concentrations is not well known, although cobalt intoxication is described in a few patients [92].

4.1. Research questions:

1) What is the relation between objectively measured physical activity and blood metal ion concentrations in patients with a metal-on-metal hip arthroplasty?

2) Are patients with an HRA physically more active than patients with a conventional stemmed THA?

3) Is objectively measured physical activity associated with patient-reported physical activity?

4) Is the outcome of revision surgery in failed MoM hip arthroplasties worse than the outcome of revision in failed non-MoM hip arthroplasties?

5) Are chronically raised metal ion concentrations associated with systemic complaints?

4.2. Outline of the thesis

The PA levels of patients with a MoM hip arthroplasty were objectively measured using wearable AMs and analysed to identify possible associations with blood metal ion concentrations. The first question is answered in chapter II and III. *Chapter II* presents patients with any type of unilateral or bilateral MoM hip arthroplasty (HRA and/or LHMoM THA), whereas *Chapter III* focuses on patients with a unilateral HRA at 10-year follow-up. To answer the second question, the unilateral HRA group presented in Chapter III was matched with a cohort of patients with a conventional stemmed THA to investigate whether PA differs between these groups (*Chapter IV*). Both groups of patients completed a few frequently used PROMs. The self-reported outcomes were compared with the results of objectively measured PA to answer the third research question in *Chapter V*. To answer the fourth research question, data of the Dutch Arthroplasty Register (LROI) were used in *Chapter VI* to compare the outcomes of revisions of failed MoM and non-MoM hip arthroplasties. The answer to the fifth research question was sought in a systematic review concerning cobalt intoxication in hip arthroplasty patients (*Chapter VII*) and in a study using a new patient-reported questionnaire on the influences of raised cobalt ion concentrations on general aspects of health (*Chapter VIII*).

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Part A

Physical Activity Monitoring
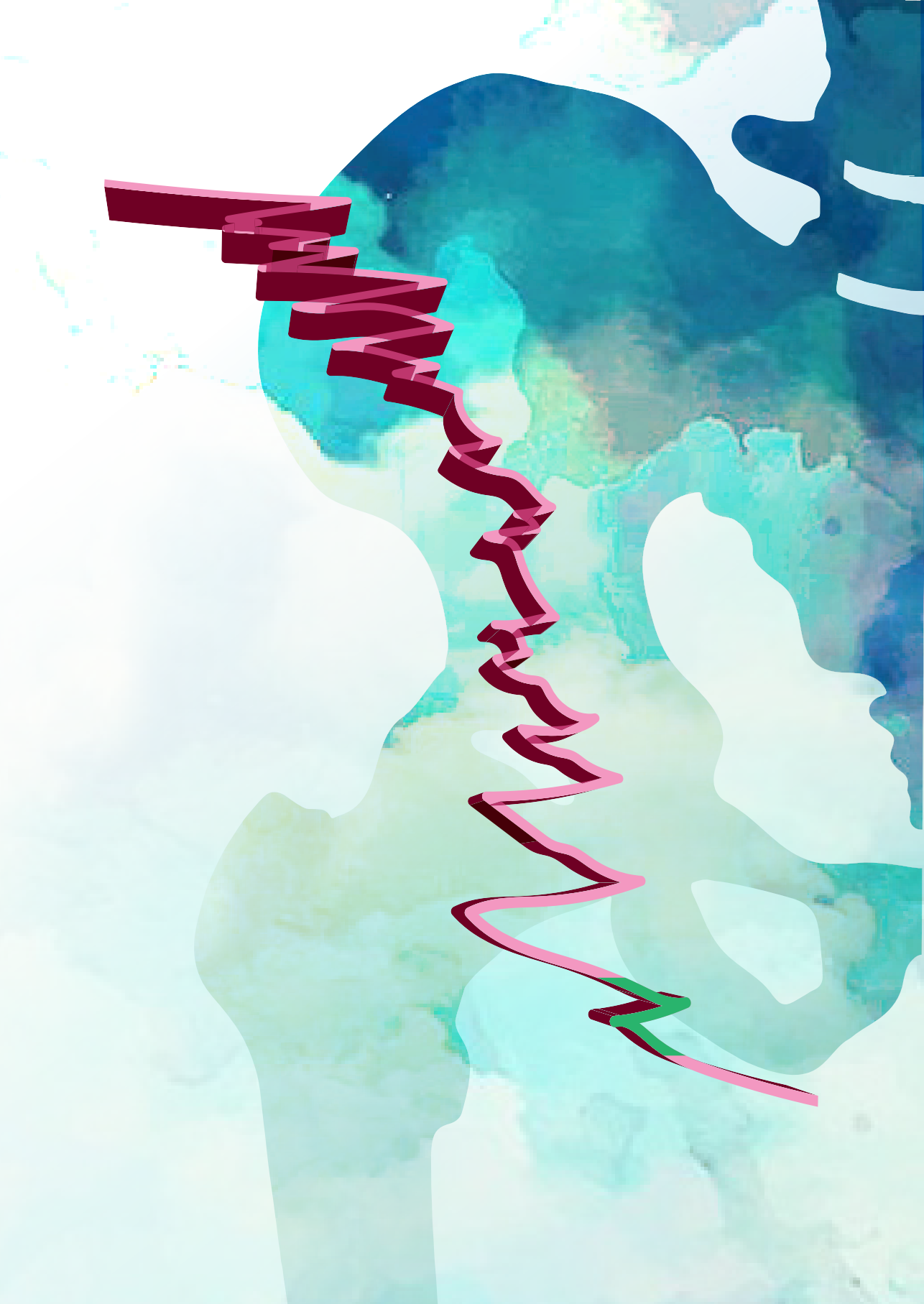
Chapter II

Metal ion concentrations after metal-on-metal hip arthroplasty are not correlated with habitual physical activity levels

Jelsma J, Schotanus MGM, Senden R, Heyligers IC, Grimm B

Hard work beats talent when talent fails to work hard

(Tim Notke / Kevin Durant)

Abstract

Introduction

Metal-on-metal (MoM) hip arthroplasties have shown high clinical failure rates with many patients at risk for a revision and under surveillance for high metal ion concentrations. Implant wear releasing such ions is assumed to be a function of use, i.e. the patient's physical activity. This study aimed to assess whether habitual physical activity levels of MoM patients are correlated with metal ion concentrations and are higher in patients with high (at risk) than in patients with low (safe) metal ion concentrations.

Methods

A cohort study was conducted of patients with any type of MoM hip prosthesis. Metal ion concentrations were determined using ICP-MS. Habitual physical activity of subjects was measured in daily living using an accelerationbased activity monitor. Outcome consisted of quantitative and qualitative activity parameters.

Results

In total, 62 patients were included. Mean age at surgery was 60.8 ± 9.3 years and follow-up was 6.3 ± 1.4 years. Cobalt concentrations were highly elevated overall (112.4 ± 137.9 nmol/L) and significantly more in bilateral (184.8 ± 106.5 nmol/L) than in unilateral cases (87.8 ± 139.4 nmol/L). No correlations were found between physical activity parameters and metal ion concentrations. Subgroup analysis of patients with low versus high cobalt concentration showed no significant differences in habitual physical activity.

Discussion

No correlation was found between physical activity levels and metal ion concentrations. Implant use by normal habitual activities of daily living seems not to influence metal ion concentrations.

Introduction

Metal-on-metal (MoM) hip arthroplasty became accepted worldwide in the early 1990s. After the first generation of MoM prostheses, improved metal alloys and manufacturing techniques made this procedure very popular. Hip resurfacing arthroplasty (HRA) was designed in particular for young and active patients [1,2]. This design was thought to produce less volumetric wear due to dynamic fluid film lubrication and the improved roundness of the two metal surfaces, which were made of an alloy of cobalt, chromium and molybdenum [2-4]. Another potential advantage was the increased stability and range of motion due to the use of larger heads [2].

Despite these improvements, concerns were raised. High clinical failure rates were observed, with adverse reactions to metal debris (ARMD) and increasing revision rates in decreasing cupsizes [5-10]. Recent studies showed that 40%-50% of patients with a MoM hip prosthesis develop a pseudotumor, with similar prevalence in well-functioning hips or painful hips. Women are affected significantly more than men [11-13].

The metal surfaces are exposed to wear, which results in the release of metal ions. Hence, the measurement of metal ions is considered an indirect measure of such volumetric wear, although the true volumetric wear can only be measured on an explanted device. Cobalt and chromium ion concentrations rise significantly after MoM implantation, with peak concentrations at 9 to 18 months postoperatively. Then an equilibrium is reached between metal ion release from the implant and metal ion release from the body (e.g. via urine) [14-16]. Rising and patient-specific metal ion concentrations after this period are thought to be due to multifactorial causes: design, acetabular component malpositioning, contact patch to rim (CPR) distance and a smaller joint size seem to play a role [9,17-21].

Physical activity (PA) and the large effect of habitual physical activity levels on general health are increasingly being recognized. PA is shown to largely reduce the risk for many chronic degenerative diseases [22,23]. Measuring habitual physical activity in the free living environment using wearable activity monitors is becoming more popular in the recent years, including in orthopaedics [24]. This technique does not have the disadvantages of the ceiling effect and the highly subjective nature of self-reported questionnaires [25]. Furthermore, an accelerometer-based activity monitor is able to differentiate between the different activity types in daily live [24].

Implant wear is also a function of use and thus of patient activity levels. In previous studies, wear of polyethylene acetabular bearings was positively related with patients' activity [26]. Studies in patients with a MoM arthroplasty also showed that intense exercise events can temporarily raise the metal ion concentrations [27-30]. Therefore it is hypothesised that daily habitual physical activity levels of patients with a MoM hip prosthesis are positively correlated with cobalt and chromium ion concentrations. This is the first study in literature studying the relation between metal ion concentrations and different types of physical activity (qualitative and quantitative parameters) and in patients with metal-on-metal hip arthroplasty using activity monitors.

Methods

A cohort study was conducted of patients with any type of MoM bearing hip prosthesis; resurfacing, Large Head MoM (LHMoM) modular total hip replacements, both unilateral and bilateral, implanted in our hospital between August 2001 and October 2012. The majority of subjects were operated and recruited in the years 2006 to 2009, when the popularity of the procedure was highest. Exclusion criteria were dementia, inactivity due to paralysis or paresis, and surgery in the past year that influenced physical activity levels.

In 220 patients, a total of 256 MoM hips were implanted, 182 resurfacing and 74LHMoM. At follow-up time, ten patients had passed away due to causes that were unrelated to the procedure or unknown (Table I). Revision surgery had already been performed in 22 patients and was planned in two patients (Table II). A total of 63 patients gave informed consent for the study. One measurement failed. Finally, data of 62 patients with 71 MoM hip arthroplasties were used for analysis (Figure 1).

Table I. Causes of Death (n=10)

Causes	Number
Unknown	5 (50%)
Pneumonia	3 (30%)
Malignancy	1 (10%)
Bleeding	1 (10%)

Table II. Reasons for Revision (n=26)

Causes	Number
Fracture	7 (25.9%)
Symptomatic MoM	5 (18.5%)
Impingement	4 (14.8%)
Unknown	4 (14.8%)
Cup Loosening	3 (11.1%)
Femoral Loosening	1 (3.7%)
Dislocation	1 (3.7%)
ALVAL	1 (3.7%)
High metal ion concentrations	1 (3.7%)
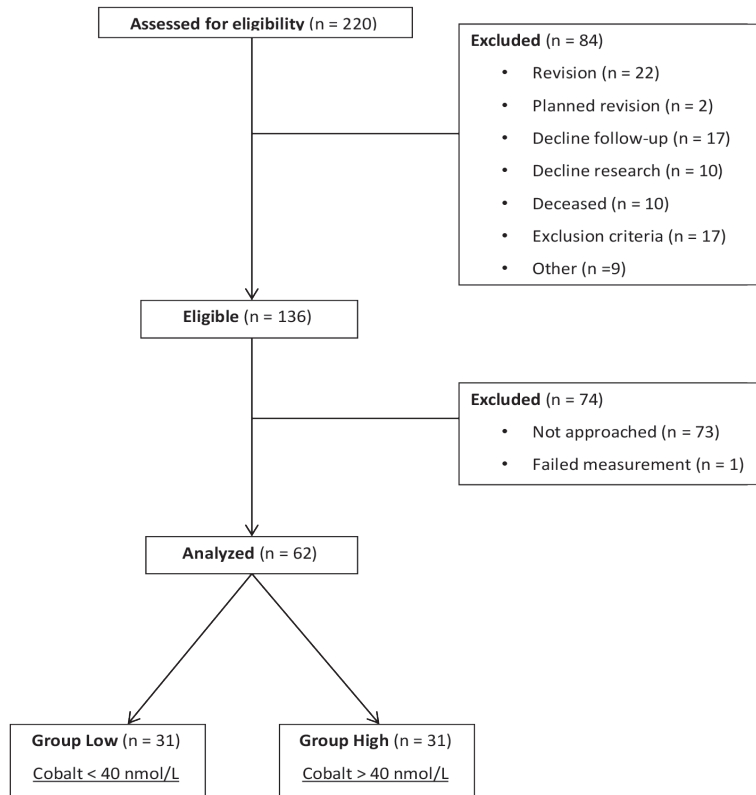
Figure 1. Diagram of the number of patients enrolled and analyzed in this study. There were two patients with a revision on one side and a reason for exclusion. Also there was one patient with a revision on one side, who did match the inclusion criteria contralaterally.

Patients' physical activity levels were assessed between October 2012 and December 2016 using anaccelerometer-based activity monitor. The implants consisted of both resurfacings and LHMoM modular total hip replacements from the manufacturers Zimmer (Durom, Warsaw, Indiana, USA) (n=25), Biomet (Recap and Mallory Head, Warsaw, Indiana, USA) (n=20) and Corin (Cormet, Cirencester, United Kingdom) (n=26).The whole patient population measured a mean age of 60.8 ± 9.3 years at surgery and a follow-up of 6.4 ± 1.4 years. Baseline characteristics for the whole group and for the subgroups are presented in Table III.

This study was performed in compliance with the 1975 Declaration of Helsinki, as revised in 2000, was studied and approved by the IRB (METC Zuyd, Heerlen, the Netherlands, IRB Nr. 10N72) and conducted in accordance with the guidelines for Good Clinical Practice (GCP).

Table III. Baseline characteristics. Numbers [proportions] and Mean [range]

Total Group		Subgroup Analysis		
		Cobalt <40 nmol/L	Cobalt >40 nmol/L	p-value
Number of subjects	62	31	31	x
Gender M/F	36/26 [58%/42%]	22/9 [71%/29%]	14/17 [45%/55%]	.077
Prosthesis resurfacing/LHMoM	40/22 [65%/35%]	26/5 [84%/16%]	14/17 [45%/55%]	< .001*
Side uni-/bilateral	53/9 [85%/15%]	30/1 [97%/3%]	23/8 [74%/26%]	.424
BMI at OR in kg/m^2	27.6 ± 3.8 [20.2 – 37.9]	27.5 ± 3.6 [21.4 – 37.9]	27.7 ± 4.1 [20.2 – 36.9]	.803
Age at OR in years	60.8 ± 9.3 [41.6 – 78.1]	56.2 ± 5.9 [43.0 – 66.3]	64.6 ± 9.8 [41.6 – 78.1]	< .001*
Follow-Up in years	6.3 ± 1.4 [3.7 – 9.6]	6.8 ± 1.4 [4.9 – 9.6]	5.9 ± 1.3 [3.7 – 9.1]	.010*
Cobalt in nmol/L	112.4 ± 137.9 [9 – 833]	25.5 ± 8.8 [9 – 38]	183.8 ± 152.8 [41 – 833]	< .001*
Chromium in nmol/L	107.8 ± 139.9 [6 – 592]	36.9 ± 19,9 [6 – 88]	165.6 ± 167.5 [15 – 592]	< .001*
Cup Size in mm	54.5 ± 3.6 [48 – 62]	55.3 ± 3.3 [48 – 62]	53.9 ± 3.7 [48 - 62]	.116
Inclination in degree	51.1 ± 7.7 [29 – 68]	50.4 ± 7.8 [38 – 64]	51.7 ± 7.7 [29 – 68]	.493

* Significance ≤ 0.05

The most recent radiographs (Standing Pelvic Anterior-Posterior (AP)) were used to determine the inclination angle of the acetabular cup. The cup inclination angle was defined as the angle between the line connecting the ischial tuberosity and the line connecting the vertices of the metal cup [31]. Cup anteversion angles were not determined for this study.

Metal concentrations were measured according to Dutch guidelines for MoM hip arthroplasty as follows: vena punction was performed by disposing the first 5mL and thereafter the blood was collected a special trace elements serum tube (BD Vacutainer 368380® Trace Element, Franklin Lakes, New Jersey, United States). The collected material was stored in a refrigerator at a temperature of 2° to 8°C and shipped to a specialized laboratory within a week at room temperature. Cobalt and chromium concentrations were determined by inductively coupled plasma mass spectrometry (ICP-MS) using the NexION® 300X ICP-MS (PerkingElmer, Waltham, Massachusetts, United States). According to the Dutch Orthopaedic Society (NOV) guidelines for MoM prostheses, a cobalt ion concentration of <40 nmol/L is considered normal and >40 nmol/L is considered increased, and patients were grouped accordingly for comparison [32].

Physical activity of subjects was measured during waking hours for four consecutive days in daily living using an acceleration-based activity monitor, which was attached to the non-affected upper leg, or least affected upperleg in case of bilateral hip arthroplasty, using a sticker. The four day measurement period was chosen based on evidence that an individual's habitual physical activity pattern can be representatively characterized by measuring activity for three to four days [33,34]. The activity monitor used (USB Accelerometer, ModelX8M-3, Gulf Coast Data Concepts LLC, Waveland, Mississippi, United States) comprises a 3-axis (14-bit, ±8g, 50 Hz) accelerometer and a 3-axis magnetometer. Data collected by means of the activity monitor was analysed in MATLAB (MATLAB R2010a, The Mathworks Inc., Natick, Massachusetts, United States) using previously validated algorithms [35]. Physical activity data per day were averaged over the four measurement days. Outcome consisted of quantitative parameters (time spent walking and cycling in seconds, the number of steps and sit-stand transfers) and qualitative parameters (cadence in steps per minute and high-intensity peak counts in numbers). This technique was clinically validated by Lipperts et al. and Van Laarhoven et al. in healthy subjects and subjects who had undergone unilateral total joint arthroplasty, using video observation as the gold standard. The studies showed an excellent accuracy (>97%) in determining activity levels with this technique in a semi-free setting [35,36]. Schotanus et al. used the same method to show, that patients

who followed an enhanced recovery pathway or an outpatient surgery pathway after total knee arthroplasty recovered equally well as patients who followed a conventional discharge protocol [37-40].

Statistical Analysis

The hypothesized relationship between blood ion levels and physical activity was investigated using Pearson's R correlations. In addition, we compared subgroups with low cobalt ion concentrations (<40 nmol/L) and high cobalt ion concentrations (>40 nmol/L) as well as subgroups with unilateral and bilateral prostheses using the independent samples T-test. For all analyses, a p-value was considered statistically significant at p≤0.05. Results are presented as mean±SD and/or range. Proportions (%) are shown if necessary. Sample size was prospectively calculated for testing a weak to moderate correlation (Pearson's R ≥ 0.40) and common α= 0.05 and β= 0.20 values requiring an inclusion of n=47 subjects. Multivariable linear regression analysis was performed to adjust for significant differences at baseline. Data were analysed using IBM SPSS Statistics 22 (International Business Machines Corporation, Armonk, New York, United States).

Results

None of the physical activity parameters showed any correlation with cobalt ion concentrations (Table IV). Pearson's correlation showed a weak, but significant, correlation between cobalt ion concentration and age at surgery (R = 0.284, p = 0.017). As expected, there was a high correlation between cobalt and chromium ion concentrations (R = 0.833). In addition, we calculated a Pearson's R correlation in patients with >10.000 steps (n = 10). Pearson's R was 0.202 (p = .575) for the correlation between steps and cobalt ion concentration.

Subjects with bilateral prostheses showed significantly (p = .009) higher metal ion concentrations (185 ± 107 for cobalt) than subjects with a unilateral prosthesis (88 ± 139) (Table V). The mean BMI was 27.6 ± 3.8 kg/m^2, mean cup size was 54.5 ± 3.6 mm and mean inclination was 51.1 ± 7.7°. These parameters did not differ significantly between subgroups with low and high cobalt concentration. Subjects walked for a mean 5404 ± 2472 seconds per day, which corresponds to 90.1 ± 41.2 minutes. Daily walking time did not differ significantly between subgroups with low and high cobalt ion concentrations (5229 ± 1956 vs 5547 ± 2840). A mean of 6694 ± 3011 daily steps were taken; the subgroup with low cobalt ion concentrations took 6909 ± 2989 steps and the subgroup with high cobalt ion concentrations took 6518 ± 3057 steps.

The low cobalt ion group scored higher on the average daily cycling time (314 ± 553 sec vs 256 ± 518 sec), but this difference was not statistically significant. Also,the low cobalt ion group's daily average values for cadence (98.5 ± 6.6 vs 95.1 ± 11.9 steps/ min) and number of high intensity peaks (88.1 ± 268.3 vs 69.9 ± 103.6) were higher, but these differenes were not significant either (Table VI).

Table IV. Pearson's R correlation for cobalt concentrations

	Pearson's R	p-value
Gender	.170	.155
BMI at OR	-.044	.782
Age at OR	.284	.017*
Follow-Up	-.205	.086
Chromium	.833	.000*
Cup size	-.039	.747
Inclination	.001	.990
Time Walk	.092	.447
Time Cycling	.227	.057
Cadence	-.202	.091
Steps	-.035	.774
Sit-Stand Transfers	-.212	.075
High Intensity	.022	.856

* Significance ≤ 0.05

Table V. Metal ion concentrations. Mean ± SD [range]

	Unilateral	Bilateral	p-value
Number of subjects	53	9	
Cobalt in nmol/L	87.8 ± 139.4 [9 – 833]	184.8 ± 106.5 [38 – 322]	.009*
Chromium in nmol/L	78.6 ± 114.0 [6 – 592]	190.5 ± 174.1 [52 – 557]	.018*

* Significance ≤ 0.05

Discussion

This study aimed to determine the relationship between habitual physical activity and metal ion concentrations in patients with a MoM hip arthroplasty, supposing that patient activity might be a factor contributing to increased metal ion concentrations. The main finding of the study was that higher activity levels

in daily live were not directly associated with increased metal ion concentrations. In this study no correlations were found between cobalt ion concentrations and the habitual level of time spent walking, time spent cycling, the number of steps and the number of sit-stand transfers in daily live. Also, no significant differences in physical activity were found between subgroups with low and high cobalt ion concentrations. The daily step count of 6694 ± 3011 steps found in this study is comparable to that of healthy people of the same age, showing that this population with an MoM prosthesis is normally active [41]. Thus, the data suggest that MoM hip arthroplasty does not limit patients with regard to habitual walking activities.

Table VI. Activity Monitoring adjusted for age at surgery, follow-up time and type of prosthesis. Mean ± SD [range].

Total Group		Subgroup Analysis		
		Cobalt <40 nmol/L	Cobalt >40 nmol/L	p-value
Time Walking in seconds	5403 ± 2472 [1646 – 17126]	5229 ± 1965 [1646 – 9288]	5547 ± 2840 [2262 – 17126]	.209
Time Cycling in seconds	282 ± 531 [0 – 2040]	314 ± 553 [0 – 1940]	256 ± 518 [0 – 2040]	.846
Cadence in steps/min	96.7 ± 9.9 [66 – 115]	98.5 ± 6.6 [81 – 112]	95.1 ± 11.9 [66 – 115]	.472
Steps number	6694 ± 3011 [1712 – 15443]	6909 ± 2989 [1712 – 14637]	6518 ± 3057 [2404 – 15443]	.568
Sit-Stand number	37.6 ± 13.5 [10 – 68]	37.3 ± 11.7 [20 – 61]	37.8 ± 14.9 [10 – 68]	.129
High Intensity Number >5.0g	78.4 ± 197.5 [0 – 1406]	88.1 ± 268.3 [0 – 1406]	69.9 ± 103.6 [0 – 408]	.981

* Significance ≤ 0.05

Our finding that metal ion concentrations were not correlated with activity levels seem to contradict previous studies that showed that intense exercise can temporarily raise the metal ion concentrations. Gleizes et al. found increased cobalt concentrations directly after a one-hour treadmill test in a two-patientstudy [27]. Heisel et al. studied the relationship between exercise and metal ion concentrations in 7 patients at an average follow-up of 17.3 months postoperatively. They found that a mean increase in activity of 28% ± 6% during a high-intensity activity week was associated with a mean decrease of 2.7% ± 4.7% in serum cobalt and a mean increase in chromium concentrations of 2.0% ± 3.0. A mean increase of 1621% ± 265% in activity on a treadmill test (acute activity) was associated with a mean increase of 3.0% ± 3.6% in serum cobalt and a mean increase in chromium

concentrations of 0.8% ± 1.7%. However, the authors noted that the values were within the variability for the measurement accuracy of these tests, so none of the differences found were significant [30]. Khan et al. did show that exercise causes a significant and immediate but temporary rise in metal ion concentrations: 13% in serum cobalt and 11% in serum chromium after one hour of exercise in 15 subjects [28]. Another study by Khan et al. showed that physical exercise raises the mean cobalt ion levels by 4.5 nmol/L (8%) within one hour of completing one hour of exercise. A longer postoperative period did not decrease the baseline cobalt ion concentration, and patients with a longer follow-up had a smaller rise in cobalt levels in response to exercise [29].

Our findings that metal concentrations are not correlated with physical activity appear to be confirmed by a case study of DeHaan et al., who reported on a triathlete with a resurfacing prosthesis and found no significant differences in cobalt blood concentrations before and after an 11-hour triathlon [42]. However, in this case study, blood samples were collected the day after the exercise, which means that it is possible that the metal concentrations had returned to their pre-exercise levels.

The above mentioned studies all included a small number of subjects (1 – 21) and showed a temporary increase in metal ion concentrations after a short-termed exercise with a cobalt ion concentration measurement immediately after the exercise. In contrast, we studied habitual physical activity levels in daily live for four consecutive days in 62 patients and found no correlations between metal ion concentrations and parameters of physical activity.This is in contrast to a recent study by Hjorth et al., which found a significant correlation between a physical activity measure and chromium ion concentrations, but not with cobalt ion concentrations [43]. Hjorth et al. used the same approach as the present study, but defined their own proprietary parameter, which may therefore be not comparable to the one used in this and other studies [35,36]. In the study by Hjorth et al., all activity was pooled into one parameter, which was defined as the sum of walking, cycling and high intensity activity measurements and expressed as a percentage of the total wearing time of the activity monitor instead of absolute numbers, as we did in this study. The surprising result of Hjorth et al. was that only chromium ion, but not cobalt ion concentrations are correlated with physical activity levels, which could be an indicator for a rather small effect size of physical activity levels on metal ion levels. Another explanation why Hjorth et al. identified a correlation between physical activity and chromium ion levels may be the fact that they assessed a significant part of a rather heterogenous patient population (e.g. 0.5 to 21 years of follow-up) during the "running-in" phase with highly transient metal ion

levels, which is a strong confounder that we deliberately excluded from analysis in our study.

Our findings show no correlation between cadence and cobalt ion concentration, which is in contrast with a study by Senden et al., who showed that a higher cadence was associated with higher polyethylene wear in patients after hip arthroplasty with a metal-on-polyethylene surface [44]. One would expect that a higher habitual walking cadence in MoM would also result in a higher wear rate, expressed by higher metal ion concentrations in the blood. However, in our study, the subgroup with low cobalt ion concentrations showed a (non-significant) trend towards higher cadence compared with the subgroup with high cobalt ion concentrations. These different findings may be due to the differences in the wear regimes of MoM bearings (dynamic fluid film lubrication) and metal-on-polyethylene surfaces (mixed mode).

The present study also found no significant correlations between cobalt ion concentrations and gender, although mean cobalt ion concentration seemed higher in women. In addition, we found no correlations between cobalt ion concentrations and BMI, follow-up, cupsize or acetabular inclination angle. As stated by Maurer-Ertl et al. and Langton et al., larger resurfacing implants seem to be more resistant to suboptimal cup position [2,9]. This is thought to be due to a thicker fluid film and a greater arc of coverage. However, the study by Maurer-Ertl et al. did not prove this higher resistance, possibly due to the small number of patients included in the study. Also, the design of the implant and the size of the component are factors that influence edge-loading, which disrupts the fluid film lubrication and thus increases wear.

Our finding that cobalt ion concentrations were not correlated with inclination angle are not in line with a study of DeHaan et al., who compared groups with different inclination angles (<55 or >55 degree) and showed that steep components had significantly higher metal ion concentrations ($p = 0.003$ for Co, $p = 0.002$ for Cr) [17]. Additionally, Van der Straeten et al. showed that patients with an acetabular component ≥ 50mm had 64% chance of being in a well-functioning group, compared to 38% for a ≤50mm component [18]. Our cohort consisted of subjects with a mean cupsize of 54.5 ± 3.6 [48 – 62] and only five patients with a 48mm cup, which is slightly below the size threshold previously investigated by van der Straten et al. The mean inclination angle was 51.1 ± 7.7 [29 – 68]. Based on the findings of Grammatopoulos et al., 22 of our subjects were not in their established inclination safezone (45 ± 10 degree) [45]. Only 1 subject in our cohort had a cup size <50mm and an inclination outside the safezone. In the current study, the risk of increased

cobalt ion concentrations due to acetabular cup malalignment or a small cup size is therefore limited.

This study does have a number of limitations. Although the calculated sample size of 47 was exceeded, as a first limitation, a weak correlation not tested for may still exist and form part of a highly multifactorial phenomenon. However, in this study, which included patients with a wide range of metal ion concentrations and physical activity levels, even the extremes did not show the hypothesized effect, so that a clinical effect or a trigger to adjust patient behavior regarding physical activity seems unlikely.

A second limitation is that activity monitoring was not performed in close and constant temporal proximity to the ion level measurement. Preferably, both assessments should have been made at the same moment of time. In our study there was a mean interval of 1.4 ± 0.8 years between physical activity monitoring and the determination of metal ion concentrations. However, as we intentionally studied habitual physical activity levels and not single peak activity events or exercise regiments, this time difference is expected not to matter, as it is accepted that a 4-day measurement is representative for an individual's general behavior over such a long period of time [33,34,46]. In addition, multiple studies show that metal ion concentrations become stable or decline in most hip arthroplasty patients after an initial running-in period of +/- 18 months [14-16]. In the follow-up of our study we measured these steady-state levels of metal ion concentrations as intended.

A third limitation of the present study is that renal functions were not measured, which may have been relevant because cobalt and chromium ions are excreted by the kidneys [47,48]. Well functioning kidneys excrete 80 to 90% of cobalt ions within days, eliminating >50% within 48 hours, and 60% of chromium ions are eliminated within 8 hours [49,50]. Measurements of metal ion concentrations were performed at variable time points during patient follow-up and the time interval to physical activity assessment was not consistent, so that physical activity in the 24h prior to blood sampling is not known. Although a highly intense activity may result in temporary peaks of metal ion concentrations, Lainiala et al. did not find any association between metal ion concentrations and mild or moderate renal insufficiency [51].

Another limitation is that this was a cohort study in a rather heterogeneous population, including patients with HRA and LHMoM, both uni- and bilateral, made by multiple manufacturers and thus with different prosthesis designs. Ion release

of these implants may not react in the same intensity to different activity levels, as this may be influenced by e.g. component clearance or by the variable arc of coverage. However, these differences may influence the slope of a relationship, but not its direction. Thus this limitation can be neglected when studying the presence of a correlation between the metal ion concentrations and physical activity levels without aiming to establish a dose-response value.

Finally, a selection bias is possible, because very active patients or more concerned patients may have been more eager to participate in this monitoring study. Further research should focus on a less heterogeneous population and thereby minimizing potentially bias.

Conclusion

Metal ion concentrations in patients with a MoM hip arthroplasty do not seem to be correlated with physical activity levels as measured in terms of walking and cycling time, walking cadence and number of steps, sit-stand transfers or intensity counts. Thus it seems that every day implant use in normal habitual activities of daily living does not increase metal ion levels and their potentially harmful effects. Apparently, wear of metal implants is too multifactorial and dominated by other factors than activity levels, or else the daily activity types measured are of a low wearing nature. In clinical practice, this study may serve to reassure metal-on-metal patients that it is safe for them to engage in daily activities like walking or cycling for general health benefit without triggering critical wear or ion release. The study also indicates that there is no need to screen highly active patients more frequently.

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2

Chapter III

Quality, but not quantity of physical activity is associated with metal ion concentrations in unilateral hip resurfacing

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You miss 100% of the shots you don't take
(Wayne Gretzky)

Abstract

Introduction
Little is known about the influence of physical activity (PA) on metal ion concentrations in subjects with metal-on-metal hip arthroplasty. Implant wear is thought to be a function of use and thus of patient activity levels. It is hypothesized that daily habitual PA of patients with hip resurfacing arthroplasty (HRA) is associated with metal ion concentrations.

Methods
Therefore a study was conducted in patients with a unilateral HRA at 10-years follow-up. Blood metal ion concentrations were determined. An acceleration-based activity monitor was used to measure PA in daily life

Results
The cohort consisted of 12 males (75%) and 4 females (25%) with a median age at surgery of 55.5 ± 9.7 years [43.0–67.9] and a median follow-up of 9.9 ± 1.0 years [9.1–10.9]. The median cobalt and chromium ion concentrations were 25 ± 13 and 38 ± 28 nmol/L. A significant association between sit-stand transfers and highintensity peaks with cobalt ion concentrations were found.

Discussion
Regarding PA and metal ion concentrations as a proxy of wear in HRA, specific activities like transfers or qualitative aspects of activity behavior like intensity, seem to matter more than the quantity of low-intensity activities like walking or cycling. This suggests that patients may safely engage in such activities to achieve important general health benefits and quality of life.

Introduction

Metal on metal (MoM) hip resurfacing arthroplasty (HRA) became a popular procedure in the 90s for young and active patients with hip osteoarthritis. The preliminary results of HRA were satisfactory and early investigators concluded a major wear reduction to safe levels [1]. Around one million procedures were performed worldwide in total [2]. Concerns about MoM implants have been raised since 2004 when metal ions were found in blood and urine of patients with MoM implants [3]. Hereafter, multiple studies and national registry data showed high failure rates and the 10-year survival rate threshold of 95% set by The National Institute for Health and Care Excellence (NICE) was not achieved [4].

During articulation, the metal surfaces are exposed to wear resulting in the release of metal ions. Indirect measure of (volumetric) wear is performed by measuring metal ion concentrations in blood, serum or urine, as direct measurment is only possible on explanted devices. After HRA a significant rise is seen in the cobalt and chromium ion concentration, with peak concentrations being reached between 9 to 18 months postoperative. After this period an equilibrium is reached between metal ion release from the implant and metal ion excretion from the body (e.g. via urine) [5-7]. Design of the prosthesis (alloy, surface), acetabular component malpositioning, contact-patch-to-rim distance (CPR) and a small joint size (e.g. in females) all seem to play a role in increased metal ion concentrations after this period [4, 8-10].

Little is known about the influence of physical activity (PA) on metal ion concentrations. Implant wear is thought to be a function of use and thus of patient PA levels [11]. Intense exercise events in patients with a MoM implants showed a temporary raise of metal ion concentrations [12-15]. With the use of wearable activity monitors (AM) it is possible to measure the habitual PA of patients in the free living environment. AMs are also able to differentiate between different PA types in daily life (e.g. stand, walk, sit). In the recent years this technique has become more popular [16].

The goal of the present study was to investigate the correlation between PA and metal ion concentrations under tight controlled conditions to minimize limitations. Therefore, we selected a homogenous group with a long follow-up assessed during a narrow time window and with close proximity of metal ion measurement and PA monitoring. The current study aims to give further evidence whether PA in general or specific behavior may be an important contributor in the explanation of increased

metal ion concentrations. It is hypothesized that daily habitual PA of patients with a unilateral HRA, measured with an AM is associated with metal ion concentrations in blood at 10-years follow-up.

Patients and Methods

A part retrospective, part prospective cohort study (Level of Evidence III) was conducted from August until November 2017. Only patients with a primary unilateral HRA with a follow-up of 10 ± 1 years per 1st of August 2017 were included. Two different approaches, posterolateral and straight lateral, and three different HRA implants were used (Table 1). Exclusion criteria were revision surgery, any type of hip arthroplasty on the contralateral side, dementia, inactivity due to paralysis or paresis and major surgery in the past year influencing PA.

Table 1. Characteristics of Resurfacing systems

	Biomet ReCap	Zimmer Durom	Corin Cormet
Radial clearance (µm)	120.93	68.23	97.67
Wall thickness at rim (mm)	3.4	4.6	5.6
Surface roughness (µm)	0.031	0.034	0.030
Mean deviation of roundness (µm)			
Head	3.2	6.1	7.3
Cup	1.9	2.5	3.8
Coverage angle (angle in °)	162° *	165°	160-166°

* In case of a femoral head size of 44 mm.

This study was performed in compliance with the Declaration of Helsinki and was studied and approved by the IRB (METC Zuyd, Heerlen, The Netherlands, IRB nr: 10N72) and conducted in accordance with the guidelines for Good Clinical Practice (GCP). Eligible patients visited the outpatient clinic for a regular check according to the Dutch Orthopaedic Society guidelines. For this study the inclination angle of the acetabular cup was determined on standardized x-ray's, standing pelvic anterior-posterior (AP) and defined as the angle between a line connecting the ischial tuberosity and a line connecting the vertices of the metal cup. The acetabular cup anteversion angle can not be reliable measured on x-ray and was therefore not determined [17].

Blood from vena punction was collected in a tube (BD Vacutainer 368380® Trace Element, Franklin Lakes, New Jersey, United States), after the first 5mL were disposed.

The collected material was shipped within a week at room temperature and stored in a refrigerator at a temperature of 2°-8°C in the meantime. Inductively coupled plasma mass spectrometry (ICP-MS) (NexION® 300X ICP-MS, PerkingElmer, Waltham, Massachusetts, United States) was used to determine cobalt and chromium ion concentrations in nmol/L [18].

An acceleration-based AM, attached to the affected leg using a skin-friendly sticker, was used to measure PA in daily life during the wake hours of four consecutive days, a common minimum period to derive a reliable estimate of habitual PA behavior [19,20]. A 3-axis accelerometer, gyroscope and magnetometer (HAM-IMU+alt, Gulf Coast Data Concepts LLC, Waveland Mississippi, United Status of America) was used to collect the raw signal which was analyzed for activity event classification in MATLAB (MATLAB R2018b, The Mathworks Inc., Natick,Massachusetts, United States) using previously validated algorithms [21].

Activity data were analyzed for the daily average values of days with at least 8 hours of AM-measuring time. Both quantitative (e.g. time spent performing different activities like walking and cycling in seconds, the number of steps and sit-stand transfers) and qualitative parameters of PA (e.g. walking cadence in steps/minute and high intensity peak counts in numbers) were collected. Acceleration vector magnitude was calculated to count and classify intensity peaks.For this study intensity peak counts were accounted for events <2g, ≥2g, ≥3g and ≥8g. This classification was chosen as events ≥2g do not usually appear during normal activities like walking but are common with impacts from e.g. sports or stumbles. The AM method used was found to work reliably in identifying activities in a semi-free setting compared to human observers, with a classification accuracy of >97% [21,22]. In addition, activity monitoring following this or similar protocols has shown its value for research and outcome assessment in current literature [23,24]. In addition, patient self-reported outcome measures (PROMs) were obtained. Patients were asked to fill in the Hip disability and Osteoarthritis Outcome Score - Physical Function Short Form (HOOS-PS) and the 12-item Forgotten Joint Score (FJS-12). The Harris Hip Score (HHS) was determined at the outward clinic by one of the authors (JJ). All three questionnaires included '100' as the best possible score.

Statistical Analysis

IBM SPSS Statistics 22 (International Business Machines Corporation, Armonk, New York, United States) was used for statistical analysis. Baseline characteristics of participants at the time of surgery (e.g. gender, age, surgical characteristics) and at the AM measurement moment (e.g. BMI, cobalt, chromium, interval LAB-AM, cup

inclination) are presented as median ± interquartile range (IQR) [range] or count and percentage.

To study the influence of baseline characteristics on cobalt ion concentrations, a linear regression analysis was performed. Also, linear regression analysis was performed to analyze the influence of PA on cobalt ion concentrations, the analysis was adjusted for age at surgery, BMI, cup size and cup inclination to obtain an estimation corrected for potential confounding factors [7,8,25]. For all analyses, a p-value was considered to be statistically significant at p ≤ 0.05

The cobalt ion concentrations in this cohort were significantly different from a normal distribution (p<.001, Kolmogorov-Smirnov test). For this reason, a linear regression analysis was performed on the cohort after excluding one subject with a very high cobalt ion concentration (428 nmol/L) as a sensitivity analysis.

Results

Between September 2003 and April 2011 a total of 182 HRA's were performed. Forty patients had a follow-up of 10 ± 1 year and were thus potentially eligble for this study. Revision surgery (n=9), bilateral hip arthroplasty (n=7) and decline to follow-up or research (n=5) were the most common reasons for exclusion. No contact could be obtained with two patients. In one subject the measurement failed, due to incorrect use of the AM. Finally, 16 patients were eligible and were included for analysis.

The cohort consisted of 12 males (75%) and 4 females (25%) with a median age at surgery of 55.5 ± 9.7 years and a range of 43.0 – 67.9 years. The median follow-up was 9.9 ± 1.0 years [9.1 – 10.9]. Three different prosthesis had been used, all with an uncemented acetabular component and cemented femoral component, with a variety of cement types (n=5). The straight lateral approach was used in 9 cases (56%) and the posterolateral approach in 7 cases (44%). The median cup size was 56 ± 4 mm [48 – 62] with an inclination angle of 52 ± 7 degrees [40 – 60]. The median cobalt and chromium ion concentration were 25 ± 10 nmol/L [13 – 428] and 38 ± 22 nmol/L [17 – 457], respectively. The interval between laboratory tests and measuring PA with the AM was 1.0 ± 1.0 days [0 – 34] (Table 2).

Table 2. Baseline Characteristics. Median ± Interquartile Range [Range] or numbers (proportions)

N of subjects	16
Gender (M/F)	12 / 4 (75% / 25%)
Age at OR in years	55.5 ± 9.7 [43.0 – 67.9]
Follow-up in years from OR	9.9 ± 1.0 [9.1 – 10.9]
Body Mass Index (BMI) in kg/m2	26.1 ± 3.8 [21.7 – 36.9]
Manufacturer	
CorinCormet	10 (62.5%)
Zimmer Durom	2 (12.5%)
Biomet Recap	4 (25.0%)
Interval lab-AM in days	1.0 ± 1.0 [0.0 – 34.0]
Cobalt in nmol/L	25 ± 10 [13 – 428]
Chromium in nmol/L	38 ± 22 [17 – 457]
Cup Size in mm	56 ± 4 [48 – 62]
Cup Inclination in degree °	52 ± 7 [40 – 60]
Approach	
Posterolateral	7 (44%)
Straight Lateral	9 (56%)
Cemented	
Acetabular	0 (0%)
Femoral	16 (100%)

The AM was worn for a median of 4.0 ± 0 days [2.0 – 4.0] with 12.4 ± 2.3 hours [10.7 – 16.2] per day. Subjects walked for 1.3 ± 0.6 hours [0.5 – 2.0] per day. A median number of 5546 ± 3286 steps [2274 – 9966] were taken per day. The cadence, defined as the amount of steps per minute, was 102 ± 13 [81 – 112] steps/minute. Sit-stand transfers were performed 39 ± 17 [21 – 74] times each day. Intensity peaks were divided in subgroups. Peaks <2.0g were detected in all patients and were counted 14669 ± 27903 [2442 – 48435] times. In six subjects the activity monitor was able to measure peaks ≥2.0g and were counted 184 ± 692 [29 – 1819] times. Further differentiated in peaks ≥3.0g (28 ± 185 [9 – 651]) and peaks ≥8.0g (2 ± 12 [1 – 40] (Table 3).

Table 3. Physical Activity Parameters as daily means. Median ± Interquartile Range [range]

AM-Measurement in days	4.0 ± 0 [2.0 – 4.0]
Total Time in hours	12.4 ± 2.3 [10.7 – 16.2]
Percentage Active in %	10.8 ± 7.0 [4.1 – 18.3]
Time Walked in hours	1.3 ± 0.6 [0.5 – 2.0]
Steps number of	5546 ± 3286 [2274 – 9966]
Sit-Stand Transfers number of	39 ± 17 [21 – 74]
Cadence in steps/minute	102 ± 13 [81 – 112]
Intensity Peaks <2.0g number of	14669 ± 27903 [2442 – 4843]
Intensity Peaks >2.0g number of	184 ± 692 [29 – 1819]
Intensity Peaks >3.0g number of	28 ± 185 [9 – 651]
Intensity Peaks >8.0 number of	2 ± 12 [1 – 40]

Regarding the association between cobalt ion concentrations and parameters of behavioral PA, a statistically significant relationship was found with cobalt ion concentrations and number of sit-stand transfers (β 5.786, 95% CI .531 – 11.041, p = .034) and also with intensity peaks ≥2.0g, ≥3.0g and ≥8.0g. This means that for any single additional sit-stand transfers a raise of almost 6 nmol/L cobalt is expected and for any single intensity peak ≥8.0g a raise of more than 10 nmol/L (Table 4).

When excluding the subject with the highest cobalt ion concentrations the linear regression analysis showed that the significant correlation between cobalt ion concentrations and number of sit-stand transfers disappeared (β .068, 95%CI -.758 - .894, P = .853). In contrast, the relationship between the cadence in steps/minute and cobalt ion concentrations showed a trend towards significance (β .753, 95%CI -.028 – 1.533, P = .057). The significant association with intensity peaks ≥2.0g, ≥3.0g and ≥8.0g were lost.

Patient self-reported outcome scores were high as commonly reported for successful total hip arthroplasty. The median scores of the HOOS-PS was 87.3 ± 27.7 [49.2 – 100.0] and 62.5 ± 39.5 [2.1 – 100.0] for the FJS-12. The Harris Hip Score showed a median score of 98.0 ± 11.0 [59.0 – 100.0].

Table 4. Results of the multiple linear regressions model describing the relationship between baseline characteristics and blood cobalt concentrations. Physical activity parameters were adjusted for age at OR, BMI, cup size and cup inclination.

Predictor	Regression Coefficient	95% CI	p-value
Percentage Active in %	1.4	-18.8 – 21.6	.877
Time Walk in hours	-45.2	-256.4 – 165.9	.639
Steps number of	-.007	-.041 - .028	.675
Cadence in steps/minute	-1.455	-11.9 – 8.9	.760
Sit-Stand Transfers number of	5.786	.531 – 11.041	.034*
Intensity peaks < 2.0 number of	.002	-.003 - .007	.337
Intensity Peaks >2.0g** number of	.233	.164 - .303	.001*
Intensity Peaks >3.0g** number of	.643	.583 - .702	<.001*
Intensity Peaks >8.0** number of	10.450	9.369 – 11.711	<.001*

* Significance at p = .005
** univariable analysis, not enough data for multivariable, adjusted analysis

Discussion

The aim of this study was to investigate the association between habitual PA during daily live and metal ion concentrations in patients with a unilateral HRA at 10 ± 1 year follow-up. The reason for increased metal ion concentrations after HRA seems multifactorial and PA might be one of the factors contributing. The current study aims to uncover an important contributor previously unknown and found a significant and clinically meaningful correlation between cobalt ion concentrations and distinct parameters of habitual PA (number of sit-stand transfers and high intensity peaks). After removal of one patient with relative abnormally high ion concentrations, also walking cadence, a proxy of walking speed, was found to have a trend towards significant correlation with cobalt ion concentrations. No significant association with cobalt ion concentrations were found for the habitual level of time spent walking, the total amount of steps and percentage of time being active.

The present study shows that qualitative parameters of PA seem more important than conventional quantitative parameters of PA. The results suggest that patients with a MoM arthroplasty can walk as long or as many steps as much as possible, without a relation with higher ion concentrations. However, if these patients walk too fast or too hard (high impacts) or have more sit-stand transfers, they are more prone to higher metal ion concentrations. Wear regimes in MoM bearings (dynamic fluid film lubrication) seem to play an essential role in these findings. After a period of sitting, the bearing surfaces might squeeze out any fluid and get into "dry" contact so that the immediate steps made after a sit-stand transfer are without fluid film lubrication, dry or mixed-mixed mode, possibly resulting in an increase in wear of the MoM articulation and subsequently higher wear and metal ion release. More sit-stand-transfers result in more steps in such a high wear mode which may explain the higher metal ion concentrations correlated with it. These results are supported by a study of Schmalzried et al. who discovered that 'wear is a function of use, not time' in total hip arthroplasty with a polyethylene bearing, but this early study could not study cadence as a proxy of walking speed or intensity [11]. Recently, it was shown that a higher walking cadence was associated with higher polyethylene wear [26]. The current study showed that wear seems not a function of any type of use, but specific types and qualitative characteristics of use. In long-term clinical follow-up, there is no evidence in current literature that high activity levels in patients with HRA result in higher revision rates. This may be due to the fact that PA is not recorded or if so, only in PROMs which have the disadvantage of being highly subjective suffering from recall bias or having a ceiling effect for activity type, duration or intensity. These limitations do not apply to wearable sensor based PA monitoring in the free living environment [27].

The current study found a high and significant correlation between cobalt ion concentrations and the number of high intensity peaks ($\geq 2.0g$, $\geq 3.0g$ and $\geq 8.0g$). Intensities are divided in low and high intensities, whereas walking and walking stairs are activities with intensity peaks $<2.0g$, but e.g. running, jumping or other events like stumbling cause intensity peaks $\geq 2.0g$. Previous studies in subjects with MoM implants showed that an acute PA, for example an hour running on a treadmill, resulted in an acute, but temporary raise in metal ion concentrations [12-15]. One hour of intense exercise is likely to result in a high number of high intensity peaks and thus an increase in metal ion release. The present findings are in accordance with these 'acute-activity' studies, but show that high intensity peaks also in daily habitual live are related to raised cobalt ion concentrations.

The influence of PA on metal wear and ion release seems insufficiently explored in current literature. The current study is in line with two studies by Hjorth et al. who also found a significant correlation between higher ion concentrations and higher PA. Hjorth et al. established this relationship for chromium but not for cobalt in their first study [28]. Considering the high correlation between both due to the metal alloy composition, this seems more an effect of statistical power (small effect size). In contrast to the current study, Hjorth et al. defined a single parameter for all activity as the sum of walking, cycling and high intensity activity measurements as a percentage of the total wearing time of the AM. Thus no differentiation by activity type, frequency, intensity and duration (time), the "FITT" components of PA as defined by the World Health Organization (WHO), was possible, a concept which was applied in the current study. A significant part of the heterogeneous patient population (e.g. 0.5 to 21-years of follow-up) was assessed during the "running-in" phase with highly transient metal ion levels. In contrast, the current study was performed with a median follow-up of 9.9 ± 1.01 years [9.09 – 10.88], far beyond the running-in phase. Another study by Hjorth et al. showed an association between PA and chromium concentrations but also with cobalt ion concentrations [29]. This study by Hjorth et al. distinguishes between activities like the current study. Walking and standing time were significantly positively correlated with cobalt and chromium concentrations, whereas sitting and lying were significantly negatively correlated. Again, a single parameter for total activity was significantly positively correlated with cobalt and chromium concentrations (Pearson's R -0.35, p = 0.004 and Pearson's R 0.44, p = 0.0002). In contrast, a correlation between high impact activities and metal ion concentrations was not found. Hjorth et al. measured activity independent of sleeping hours and wear time. We prefered the absolute definition of PA parameters as most commonly reported. Long and/or short sleeping time would create large variations in Hjorth's definition of PA levels and the observed effects may be due to more sleeping hours rather than increased PA.

The present results appear in contrast to our previous study, where no correlation between habitual PA and metal ion concentrations was found in a cohort study of 62 patients [30]. Also, no significant differences in PA were found between groups with a low (<40 nmol/L) and a high (>40 nmol/L) cobalt ion concentration. This study was performed with a heterogeneous cohort including subjects with HRA, large head MoM total hip arthroplasties, both uni- and bilateral which may have confounded the correlations. In a similar fashion, the large mean interval of 1.4 ± 0.8 years between determining PA with the AM and determining metal ion concentrations may have reduced the statistical power for detecting a correlation. In contrast, the current study was performed in a cohort with subjects at the same

time of follow-up with a unilateral HRA. The median interval between determining metal ion concentrations and PA monitoring was minimized and equal (1.0 ± 0 days [0 – 34]). Based on the PROMs one may assume that a representative group was selected and analysed.

The current study does have its limitations. First, although we reduced the heterogeneity compared with our previous study, this cohort consists of subjects operated with one out of three different implants, placed by two different approaches. Different implants are likely to be designed differently, including different composition. This was thought to be the reason for increased metal ion concentrations [31]. These implants may not react in the same intensity to different PA levels and thus influence the level of metal ion release. Stratifying analyses by implant type would not be feasible due to the limited sample size. It is known that a low surface roughness and high sphericity improve the wear behavior because this allows for a better fluid film lubrication. The implants used in the current study were not completely comparable according to design. However, the activity driven wear mechanisms would be similar but just different in effect (Table 1) [32]. The slope of relationship between PA and metal ion concentrations might be influenced hereby, but this is unrelated to direction.

Compliance in wearing of the AM seems good considering the 80% of subjects carrying the AM for 4 days with a median wear time of 12.4 ± 2.3 hours per day. The AM was worn for less than four days in a minority of subjects (20%) and one measurement failed. Further improvements should focus on increasing the compliance and optimize results by an easy to use AM with a long battery time (>4 days).

Thirdly, the cohort became rather small because of the strict inclusion criteria and only in six subjects the AM was able to detect intensity peaks >2.0g. The linear regression analysis for the association between these intensity peaks and cobalt ion concentrations was performed univariable because of the limited available data. Also, the metal ion concentrations were not normally distributed. One subject showed abnormal high cobalt ion concentrations of 428 nmol/L. The correlations between PA and cobalt ion concentrations were affected after excluding this subject. The same patient also showed a high number of sit-stand transfers and the most high intensity peaks, up to 10-20 times more than other subjects. The patient did not stand out with respect to other parameters. For instance, the implanted cup size was 52 mm, and the degree of inclination was 49. This patient was eligible for inclusion, and therefore included in the primary analysis. The reason that we performed additional analyses excluding this patient only served as a sensitivity

analysis because of this abnormal value. This way, the intended reader can judge the effect of this single extreme observation on the conclusions of the manuscript. This finding itself was the reason to perform this study and highlights the question again. Further research should focus on patients with high metal ion concentrations and the correlation with PA, high intensity peaks in particular.

The present study showed that a higher number of sit-stand transfers and a higher number of high intensity peaks are significantly associated with higher metal ion concentrations. At the same time, the daily time spent walking and the number of steps as common quantitative measures of PA behavior did not show an association with metal ion levels. It seems that general habitual PA like normal walking and stepping does not or only slightly influences metal ion concentrations. Only behavior (many STT) and qualitative aspects of PA (high intensity, fast walking) matter. For patients it seems safe to engage in activities with low intensity peaks like walking or cycling without triggering critical wear or metal ion being able to achieve important general health benefits and quality of life.

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3

Chapter IV

Patients with hip resurfacing arthroplasty are not physically more active than those with a stemmed total hip

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Never say never because limits, like fears, are often just an illusion

(Michael Jordan)

Abstract

Introduction
Hip resurfacing arthroplasty (HRA) was designed for the highly active patient because of the various theoretical advantages compared with stemmed total hip arthroplasty (THA), but has shown high failure rates. Physical activity (PA) after arthroplasty is frequently determined with the use of questionnaires, which are known for their subjective nature, recall bias, and ceiling effect.

These disadvantages are not applicable to physical activity monitoring (AM) using sensors. We compared objectively measured PA at long-term follow-up in a matched cohort of HRA and stemmed THA subjects

Methods
We compared 2 groups of 16 patients (12 males) in each group, one having received unilateral HRA (median age 56 years at surgery) and a matched group having received unilateral stemmed THA with a small diameter femoral head (28 mm) on conventional polyethylene (median age 60 years at surgery) with osteoarthritis as indication for surgery, 10 years after surgery. Groups were matched by sex, age at surgery, and BMI. The daily habitual PA was measured over 4 consecutive days in daily living using a 3-axis accelerometer, gyroscope, and magnetometer. Both quantitative parameters (time standing, sitting, walking, number of steps, and sit–stand transfers) and qualitative parameters (walking cadence) were determined

Results
The AM was worn for a median 13 (11–16) hours per day. The median daily step count was 5,546 (2,274–9,966) for the HRA group and 4,583 (1,567–11,749) for the stemmed THA-group with 39 (21–74) versus 37 (24–62) daily sit–stand transfers respectively. The other PA parameters were also similar in both groups.

Discussion
We found similar median PA levels and also identical ranges. While short-term effects may exist, ageing and related behavioral adaptations or other effects seem to render the theoretical activity benefits from HRA irrelevant at longer follow-up.

Introduction

Metal-on-Metal (MoM) hip resurfacing arthroplasty (HRA) was designed for the highly active patient because of various theoretical advantages compared to conventional stemmed MoP-THA: low volumetric wear, large physiological diameter femoral heads offering stability, near-natural joint kinematics and increased range-of-motion compared to small-diameter THA and preservation of the femoral bone [1]. HRA was commonly advertised as 'the sporting hip' and publicity was created with subjects participating in triathlons after HRA [2]. Gait analysis studies showed that HRA subjects returned to a more normative gait pattern with a higher walking speed when compared with THA [3, 4]. HRA showed initially promising results, however since 2004 concerns raised, because of high failure rates. In The Netherlands the use of HRA is forbidden by the Dutch Orthopaedic Society (NOV) and Government since January 2012 [5].

It can be expected that patients who received a HRA would be more physically active after surgery when compared to patients who received a stemmed THA with a small-diameter MoP or ceramic-on-polyethylene (CoP) bearing for multiple reasons: the theoretically better implant design features of HRA listed above claiming to support a more active lifestyle, the selection of patients for this particular implant (young and active) and the related patient expectations (high pre-operative demands on post-operative activity). A few studies have investigated return to sports after HRA and showed that patients were able to return to high activity levels and sporting activities postoperatively, at least at short time follow-up [6, 7]. Some studies comparing a HRA with a stemmed MoP- or CoP-THA showed higher postoperative activity levels after HRA 3-4 years follow-up. However, activity levels were determined using a (weighted) self-reported activity questionnaire [8, 9]. The highly subjective nature, strong recall bias and possible ceiling effect are known disadvantages of such questionnaires especially for quantifying activity levels, which is in contrast to activity monitoring (AM) using sensors [10]. Wearable AMs measures a patient's habitual physical activity (PA) objectively and continuously in the free living environment and different physical activities can be differentiated [11, 12]

We investigated objectively measured PA at long-term follow-up in an age and sex matched cohort of HRA and stemmed THA subjects. The hypothesis was that subjects with a unilateral HRA are physically more active in habitual daily live, measured by AM.

Patients and methods

We conducted a cohort study at the Zuyderland Medical Centre, Sittard-Geleen, The Netherlands between August and November 2017 (recruitment of HRA-group) and from February to June 2018 (recruitment of stemmed THA-group). We compared 2 groups, one having received unilateral HRA and a matched group having received unilateral stemmed THA with a small diameter metal or ceramic femoral head (28mm) on conventional polyethyelene with osteoarthritis as indication for surgery. The HRA-group with a median follow-up of 10 [9 – 11] years was initially conducted for another study, the methods of which are described in detaill elsewhere [13]. The stemmed THA-group was matched by sex, age at surgery, follow-up since surgery and BMI. Patients with an uncemented, unilateral stemmed THA with a MoP- or CoP-bearing were included. The follow-up was set on 8 – 12 years to optimize the chances of a matched cohort. Finally, 16 patients consented to the study and were included as a matched cohort (Figure 1). There were no statistically significant differences between group characteristics at baseline (Table 1). The use of the AM has been described in detail elsewhere [11]. The daily habitual PA was measured during waking hours for 4 consecutive days in daily living. The AM used to collect the raw signal was a 3-axis accelerometer, gyroscope and magnetometer (HAM-IMU+alt, Gulf Coast Data Concepts LLC, Waveland Missipi, United Status of America). The data received with this AM was analyzed with MATLAB (MATLAB R2017a, The Mathworks Inc., Natick, Massachusetts, United States) with the use of previously validated algorithms with an excellent accuracy (>97%) in determining PA levels in a semi-free setting [11]. With the AM various quantitative parameters of PA can be obtained and in this study we assessed the following metrics: the time in hours standing, sitting, walking and cycling and the amount of steps and sit-stand-transfers taken. Walking cadence, defined as the number of steps per minute and a proxy of walking speed, was calculated as a qualitative paramater.

We also assessed outcome by 3 commonly used patient-reported-outcome-measures (PROMs): the 12-item Forgotten Joint Score (FJS-12) and the Hip disability and Osteoarthritis Outcome Score Physical Function Short Form (HOOS-PS), both with '100' as the best possible score and the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) to determine a total activity score [14-16].
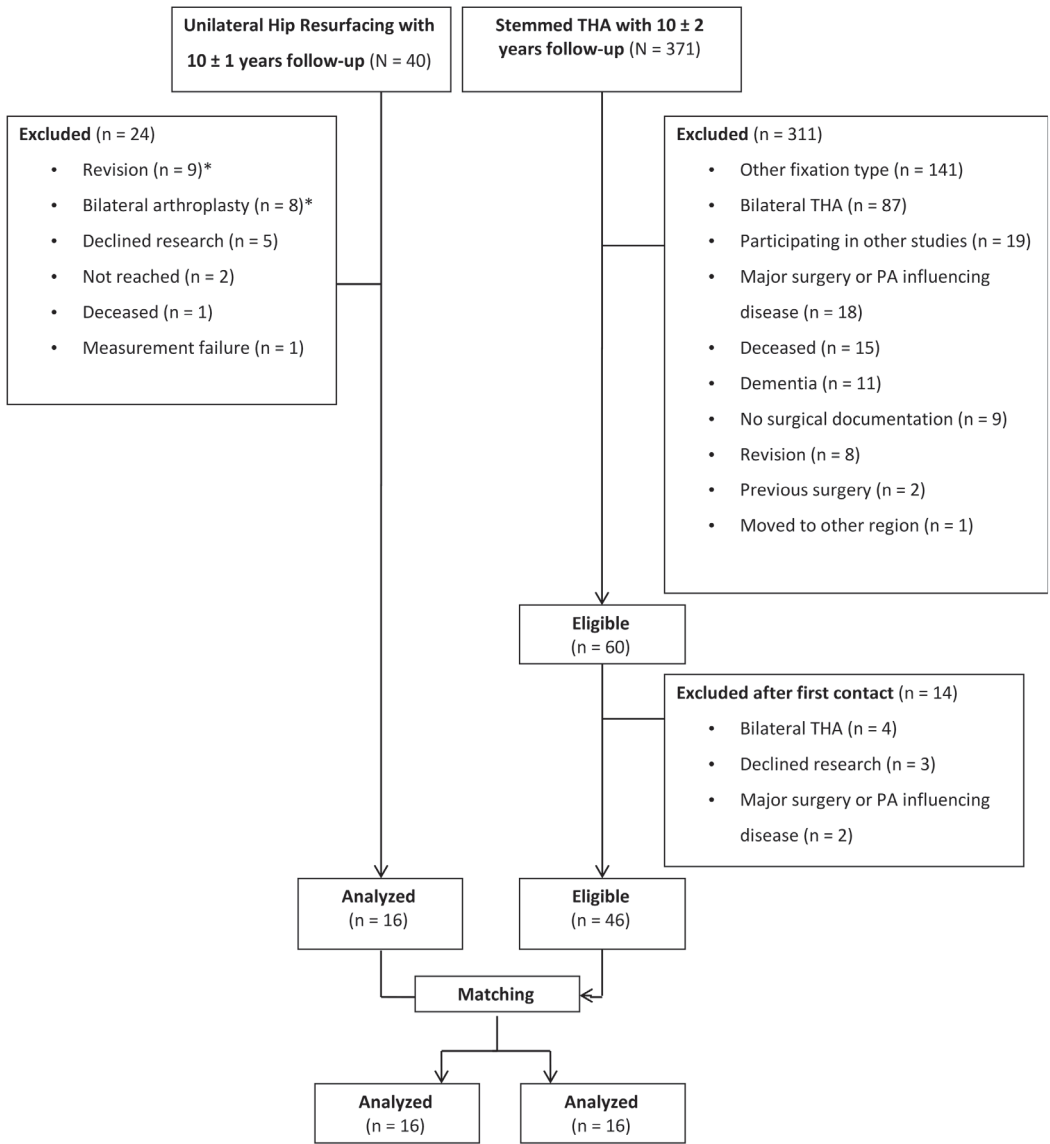
Figure 1. Diagram of the number of patients enrolled and analyzed in this study.

This study was performed in compliance with the 1975 Declaration of Helsinki, as revised in 2013 and was studied and approved by the IRB (METC Zuyd, Heerlen, The Netherlands, IRB nr: 10N72 + amendment) and conducted in accordance with the guidelines for Good Clinical Practice (GCP). All patients signed informed consent. The authors declare they do not have any kind of conflict of interest.

Statistics

Group comparison (e.g. patient characteristics) and parameters of PA between the groups were performed using the Mann-Whitney U test, because of the small groups, Pearson's chi-square test and, in case of expected cell-counts, Fisher's exact test were used to test for differences between groups present at baseline. For all analyses, a p-value was considered to be statistically significant at P≤0.05. Results are presented as median [range]. IBM SPSS Statistics 22 (Armonk, New York, United States) was used for statistical analysis.

Results

Groups had similar baseline characteristics (Table 1) and showed similar PA monitor parameters (Table 2) and PROMs (Table 3).

Table 1. Baseline Characteristics. Median [range]

		HRA-Group	Stemmed THA-Group	P-value
Sex (M)		12	12	1.0
Age at Surgery (yr)		56 [43 – 67]	60 [53 – 68]	0.1
Follow-up (yr)		10 [9 – 11]	10 [8 – 12]	0.4
BMI (kg/m^2)		26.1 [22 – 37]	29.0 [20 – 40]	0.1
Approach	Posterolateral	7	7	1.0
	Straight Lateral	9	9	
Bearing	MoM	16 (100%)	-	-
	MoP	-	4 (25%)	-
	CoP	-	12 (75%)	-

MoM = metal-on-metal, MoP = metal-on-polyethylene, CoP = ceramic-on-polyethylene

Table 2. Parameters of Physical Activity Monitoring. Median [range]

	HRA-Group	Stemmed THA-Group	P-value
Total AM-wearing time (hr)	12.4 [10.7 – 16.2]	14.3 [10.5 – 16.0]	0.1
Time Sitting (hr)	7.6 [4.6 – 12.0]	9.6 [3.8 – 12.7]	0.1
Time Standing (hr)	3.0 [1.8 – 5.7]	3.0 [1.6 – 6.2]	0.9
Time Walked (hr)	1.3 [0.5 – 1.9]	1.1 [0.4 – 1.8]	0.6
Time Cycled (hr)	0.05 [0.0 – 0.48]	0.01 [0.0 – 1.2]	0.5
Steps taken (number)	5546 [2274 – 9966]	4583 [1567 – 11749]	0.6
Sit-Stand-Transfers (number)	39 [21 – 74]	37 [24 – 65]	0.7
Cadence (steps/minute)	102 [81 – 112]	98 [80 – 110]	0.3

Table 3. Patient Reported Outcome Measures

	HRA-Group	Stemmed THA-Group	P-value
HOOS-PS	87 [49 – 100]	67 [49 – 100]	0.3
FJS-12	63 [2 – 100]	56 [4 – 100]	0.5
SQUASH	6150 [1110 – 18480]	4560 [1050 – 9300]	0.2

Discussion

This observational matched-cohort study showed that patients with a unilateral HRA are not physically more active when compared to subjects with a unilateral stemmed MoP- or CoP-THA at 10-years follow-up. This is counterintuitive to expectations, as HRA patients received the theoretical advantages of the implant design (large, near physiological head diameter), surgical procedure (anatomical preservation) and represent a selection bias towards subjects presenting, being perceived by the surgeon or themselves expecting to be more physically active and demanding than patients in the stemmed conventional MoP/CoP small-diameter head THA-group. In addition, in this matched-cohort study, the median age and BMI was higher, but not significant, in the stemmed THA-group both established to be related with a less active lifestyle. Patients with both types of implants did not only have comparable mean PA levels but also showed identical ranges. Thus it seems that both implant types enable the same level of PA and that activity levels rather depend on individual lifestyle than on implant type, at least at 10-years follow-up.

PA is considered a major risk factor for a number of adverse health outcomes. Reaching a daily step count >8000 has been associated with a lower risk of all-cause mortality [17]. In our study 13 subjects (5 HRA, 8 stemmed THA) made <5000 steps/

day, 5 subject ≥8.000 steps/day (2 HRA, 3 stemmed THA) and only 1 subject >10.000 steps/day (HRA). This suggests that almost half of the patients in this study would be considered living sedentary lifestyles with the associated risks of developing non-communicable diseases [18]. Sedentary time as a parameter is related to but largely independent of PA levels and was numerically higher in THA than HRA (p=.05), but this absolute time difference corresponds almost completely with the difference in total wear time between both groups, indicating more a difference in instructions or compliance to it for wear time (waking hours) than activity behavior.

The groups showed no statistically significant differences in the HOOS-PS and FJS-12, suggesting that the groups are comparable according to the assessed domains such as pain, patient satisfaction or perceived function. A 20-point mean difference was seen in the HOOS-PS in favor of HRA. This is in accordance with a recent publication of Oxblom et al. [19]. They studied 726 subjects 7-years after primary HRA or conventional THA showing a significant difference in HOOS subscales of function of daily living and function in sport and recreation, although HOOS subscales of symptoms, pain and quality of life, EQ-5D index and visual analog scores for pain and satisfaction did not differ.

It has been shown that patients 1 year after receiving stemmed THA only show little changes in objectively measured free-living PA compared with preoperative levels [20, 21]. While the reason not to use a pain-free hip and improved functional capacity towards higher PA levels is multifactorial, one possible explanation is that, as PA levels are known to be related to wear of MoP bearings, long-term participation in high impact activities is usually not recommended [22]. However, there is only little prospective evidence reporting a poor clinical outcome with higher levels of activity [23]. In Danish and American guidelines and a Dutch survey most low-impact activities were only allowed, though not necessarily promoted post-THA [24]. This is in contrast with the advice given by orthopaedic surgeons to HRA patients and the publicity of HRA manufacturers calling it a 'sporting hip'. Multiple studies have shown a high return to sport, including high intensity activities such as long-distance triathlon, after HRA [2, 25]. For subjects with a conventional THA this has not been advised but may be possible.

The studies in current literature comparing PA or sports participation in HRA and stemmed THA have all been performed using (weighted) PA questionnaires [8, 9]. Our study is one of the first in its kind to evaluate habitual PA in the free living environment by a wearable AM. Questionnaires are limited by the highly subjective nature and ceiling effect, which is in contrast to the objectively

results by AM [10]. Zywiel et al. performed a study comparing PA, measured by a weighted questionnaire (comparable with the SQUASH), in HRA and matched cohort of patients with a stemmed THA [8]. At final follow-up (3-4 years) the HRA-group had a higher mean weighted activity score than the stemmed THA-group (p < 0.01), while activities preoperative were similar. It was not described if there were differences regarding the instructions for postoperatively approved (high intense) PA. Other comparison studies by Pollard et al., Vail et al. and Mont et al. used UCLA activity scores and weighted activity scores and found a higher degree of PA in HRA, although these studies have numerous limitations mainly related to the uncontrolled bias of HRA towards very high pre-operative PA levels [9, 26, 27]. Our study has limitations. The number of subjects was rather low. The main cause for this was the initially strict inclusion criteria for the initial HRA study [13]. Another limitation was that no objective information, e.g. PA monitoring data, was available of the preoperative setting of the subjects. This might have influenced our results, because the physically more active patients could have been indicated for hip resurfacing at the time of surgery, and thus, selection bias may have occurred. However, such a possible selection bias would further support the finding of this study.

Conclusion

This is the first study comparing postoperative PA levels between HRA and stemmed THA using wearable sensors for objective PA measures. HRA theoretically supports high PA levels, by design and surgery, which should result in a difference at 10-years, although this study found no differences in PA and even ranges are comparable. Even well-reasoned theoretical advantages about functional advantages of any implant design require clinical validation and should not be assumed for indication (especially at risk of a disadvantage). While short-term effects may exist, ageing and related behavioral adaptations or other effects seem to render the theoretical activity benefits from HRA irrelevant at longer follow-up. PA levels at long follow-up seem to depend less on implant type but on other factors warranting further research to ensure the related health benefits in THA patients.

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4

Chapter V

Only limited correlations between patient-reported outcomes and objectively monitored physical activity 10-years after THA

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It's not whether you get knocked down, it's whether you get up

(Vince Lombardi)

Abstract

Introduction
In orthopaedics, patient reported outcomes (PROMs) are designed to quantify changes in pain and to assess physical function, most often after joint arthroplasty. However, PROMs have some disadvantages; most important is their subjective nature. The aim was to investigate how patient-self-reported-outcomes of general health, disease-specific outcome and physical function, joint-awareness and self-perceived activity levels are correlated with objectively-measured physical-activity (PA) parameters derived from wearable activity-monitors (AM) in subjects with a hip-arthroplasty.

Methods
A prospective cohort study was conducted in a group of 32 patients, with a mean follow-up of 10 years after total hip arthroplasty. To assess different domains, the SF-36 (general health), HOOS-PS (pain/functional outcome), FJS-12 (joint awareness) and SQUASH (physical activity) were chosen. Activity-monitoring was performed using a 3-axis accelerometer, gyroscope and magnetometer.

Results
No significant correlations between PA-parameters and the FJS-12 and SQUASH were found. The HOOS-PS was significant correlated with BMI, the daily time walking and total-time active and the amount of daily steps. The physical functioning-subscale of the SF-36 was significant negative correlated with BMI and time sitting, but significant positive correlated with time walking, total-time active and the amount of daily steps.

Discussion
Considering the value of PA for maintaining general health, the value of using sensor-based AMs to assess efficacy of treatments in this health related dimension or use it as a tool for patient education, awareness and communication, seems very high.

Introduction

Physical activity (PA) is recognised as an important factor for health benefits. The World Health Organization (WHO) has developed public health-oriented PA guidelines because physical inactivity is a risk factor for chronic diseases and premature mortality [1]. To quantify PA, multiple techniques are used that can be divided into direct methods (e.g. accerelometers) and indirect methods including questionnaires retrospectively collecting patient perceptions of an outcome dimension [2]. Patient Reported Outcome Measures (PROMs) are used to quantify a disease state or interventional outcome as perceived by the patient, potentially improving care [3]. PROMs are available to measure pain, satisfaction, psychological dimensions such as kinesophobia or awareness and also PA. In orthopaedics, PROMs are designed to quantify changes in pain and to assess physical function (PF), most often after joint arthroplasty [4,5]. The International Society of Arthroplasty Registries (ISAR) stated that PROMs are the best objective tool currently available to evaluate patient-centered outcomes [6]. While commonly used, PROMs can suffer from their subjective nature, recall bias, ceiling effects, time consuming methodology, low response and completion rate or transcription errors [7-10].

Objective function can be assessed by performance tests such as the 'Timed-Up and Go-test (TUG)' or gait analysis in a biomechanic laboratory, but also by activity monitoring in daily life capturing PA behavior (e.g. number of steps) and qualitative aspects of PA (e.g. steps per minute). Self-reported PF and objectively measured function after total hip (THA) or knee arthroplasty (TKA) are increasingly reported in the literature before and at various time points after surgery, but also shows the limitations of PROMs [11]. Within the first 3-weeks after THA or TKA patients report improved PF (HOOS & KOOS), but this was not correlated with objectively assessed PF (paced-walk, chair-stand,stair-climb tests)[12]. Also, at 4-months follow-up self-reported PF (HOOS & KOOS) improved significantly whereas performance-based function (30-second chair stand-test) improved only slightly [13]. HOOS scores one year after THA were not in line with objectively measured improvements in performance-based function and gait [14].

Wearable activity-monitors (AMs) are able to differentiate between different PA types in the free living environment (e.g. stand, walk, and sit). The major purpose and patient expectation of THA is the reduction in pain and restoration of function. It is unknown if and how PROMs after THA reflect levels or qualitative aspects of PA in daily life as captured with wearable AMs. The aim of this study was to investigate how PROMs of various dimensions, general health, disease specific outcome and in

particular PF, joint awareness and self-perceived activity levels are correlated with objectively measured PA parameters derived from wearable AMs in subjects with a hip arthroplasty.

Material and Methods

A prospective cohort study was conducted between August 2017 and June 2018. First, patients with a primary unilateral hip resurfacing arthroplasty (HRA) at 10 ± 1 year were included. A total of 40 patients were eligible, but 24 were excluded, among them 9 revisions and 8 declines in follow-up/research. The other group of patients received a unilateral stemmed THA with a small diameter femoral head (28mm) on conventional polyethyelene with osteoarthritis as indication for surgery. This group was matched with the HRA-group for sex, age at surgery, follow-up since surgery (8-12 years) and BMI. The groups were initially included for another study, the methods of which are described in detail elsewhere [15]. For the current study all data were merged. This study was conducted in accordance with the Good Clinical Practice (GCP)-guidelines and performed in compliance with the 1975 Declaration of Helsinki, as revised in 2013. The study was approved by the IRB (METC-Z, Heerlen, The Netherlands, IRB: 10N72 + amendment). All included patients signed informed consent.

Activity monitoring was performed and PROMs were collected at one moment in follow-up, close to 10-years follow-up (8-12 years). A 3-axis accelerometer, gyroscope and magnetometer (HAM-IMU+alt, Gulf Coast Data Concepts LLC, Waveland Missipi, United States) was used. The AM was applied on the lateral side of the affected upper-leg using skin-friendly tape. Patient's habitual PA patterns can be representatively characterized by measuring activity for 3-4 days [16,17]. PA was measured during waking hours for four consecutive days in daily living with a minimum of 8h per day. The raw signal received with this AM was analysed using published algorithms in MATLAB (MATLAB R2017a, The Mathworks Inc., Natick, Massachusetts, United States). This approach has been previously described and validated in a semi-free setting and achieved an excellent accuracy (>97%) in determining PA levels in healthy subjects and subjects after unilateral total joint arthroplasty [18,19].

The PROMs used in the current study were chosen to assess different domains and thus to study their respective correlation with objective levels and qualitative aspects of PA: general health (SF-36), pain and functional outcome (HOOS-PS),

joint awareness and satisfaction (FJS-12) and physical activity (SQUASH). The 36-item short-form (SF-36) was constructed to survey health status and designed to use in clinical practice and research. It includes eight health concepts: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. For all subscales 100 is the best score and 0 the least. Only the subscale physical functioning (PF) was used [20]. The disability and Osteoarthritis Outcome Score - Physical Function Short Form (HOOS-PS) is a validated measure of physical function. The score ranges from extreme difficulties (0) to no difficulties (100) in physical function [21,22]. The 12-item Forgotten Joint Score (FJS-12) was designed to evaluate the patients' ability to forget about a joint as a result of a successful treatment. It consists of 12 questions about awareness of an artificial joint with five answer possibilities ranging from never to mostly. The FJS-12 is validated and was shown to have a high internal consistency and a low ceiling effect [23]. The score ranges from 0 (worst) to 100 (best). The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) is a questionnaire to measure PA. The domain scores were calculated by multiplying the number of minutes per week with an intensity score (range 1-9) which is based on the reported intensity combined with the classification according to Ainsworth's Compendium of Physical Activities [24,25]. The sum of the scores per domain is the total activity score, which was used for this study. In order to reach sufficient content validity, van Poppel et al. recommended that at least duration and frequency should be determined by a questionnaire assessing total PA and should also cover PA in all settings during daily life [26]. This is in accordance with the FITT components established by the WHO (frequency, intensity, type and time). In light of this recommendation, the SQUASH was the only questionnaire in the current study to specifically assess PA and able to determine if patients meet recommendations for PA [27]. No funding was obtained.

Statistical analysis

Parameters of PA and results of the PROMs were averaged for the whole cohort and reported as mean ± standard deviation (SD) [range] or with numbers and proportions (%). Pearson's correlation coefficient (r) was computed to quantify the correlation between parameters of PA and results of PROMs. Correlations of 0.20-0.39 were considered 'weak', 0.40-0.59 'moderate' and 0.60-0.79 'strong' [28]. No multivariate analyses were performed because the goal was to show the degree of linear relationship between two continuous measures (e.g. PROMs and PA). For all analyses, a p-value was considered to be statistically significant at P≤0.05. IBM SPSS Statistics 22 (International Business Machines Corporation, Armonk, New York, United States) was used for statistical analysis.

Results

A total of 32 subjects with 32 hip arthroplasties were included. Baseline characteristics (e.g. BMI, age) and follow-up time are summarized in Table 1.

The results of the PROMs and parameters of PA monitoring, all showing large value ranges, are shown in Table 2 and 3. Correlation coefficients were computed for PROMs with baseline characteristics and PA parameters. No significant correlations were found for the FJS-12. The HOOS-PS was statistically significant correlated with BMI (negative correlation), the daily time walking, the daily total time active and the amount of daily steps. The SQUASH was only statistically significant negative correlated with the age at surgery, but not with any of the objectively measured PA parameters. The PF-subscale of the SF-36 was statistically significant negative correlated with BMI and the time sitting, but statistically significant positive correlated with the time walking, the total time active and the amount of daily steps (Table 4).

Table 1. Baseline Characteristics

Sex	24 M (75%) - 8 F (25%)
Age at Surgery (years)	57.8 ± 5.7 [43.0 – 68.0]
Follow-Up (years)	9.9 ± 0.9 [8.5 – 11.8]
BMI (Kg/M^2)	28.2 ± 4.9 [20.4 – 39.8]

Table 2. Results of PROMs

SF-36 PF (n=32)	70 ± 22 [25 - 100]
HOOS-PS (n=25)	77 ± 19 [49 – 100]
FJS-12 (n=31)	56 ± 31 [2 – 100]
SQUASH (n=29)	5744 ± 4103 [1050 – 18480]

Table 3. Parameters of Physical Activity Monitoring

AM wearing days	3.6 ± 0.7 [2 – 4]
Total measured time (hours)	13.1 ± 1.8 [10.5 – 16.2]
Time sitting (hours)	8.4 ± 2.2 [3.8 – 12.7]
Time standing (hours)	3.3 ± 1.3 [1.6 – 6.2]
Time walking (hours)	1.2 ± 0.5 [0.4 – 2.2]
Time cycling (hours)	0.2 ± 0.3 [0.0 – 1.2]
Total time active (%)	10.4 ± 4.4 [3.4 – 20.0]
Sit-Stand Transfers (number)	40 ± 13 [21 – 74]
Steps (number)	5434 ± 2566 [1567 – 11749]
Cadence (steps/min)	98 ± 10 [80 – 112]
Intensity Peaks <2.0g (number)	27135 ± 20741 [2442 – 85974]
Intensity Peaks >2.0g (number)	886 ± 1670 [0 – 8097]

*Daily values except AM wearing days and cadence

Table 4. Pearson's R correlation

	HOOS-PS	SQUASH	FJS-12	SF-36 PF
Age at surgery	-.031	**-.592****	.226	-.310
BMI	**-.590****	-.041	-.358	**-.537****
Time sitting	-.395	-.208	-.034	**-.407***
Time standing	.267	.211	.021	.327
Time walking	**.498***	.273	.260	**.500****
Time cycling	-.042	-.006	.030	.144
Total time active	**.447***	.247	.229	**.524****
Sit-Stand Transfers	-.065	-.333	.063	-.081
Steps	**.408***	.199	.209	**.445***
Cadence	.172	.198	.134	.345
Intensity Peaks <2.0g	.149	-.050	.228	.165
Intensity Peaks >2.0g	.142	-.031	.265	.118

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

Discussion

The aim of this study was to investigate the correlation between PROMs of different outcome dimensions and objectively measured PA in daily life with the use of a wearable AM in subjects 10-years after unilateral hip arthroplasty. The main finding of this study was that objectively measured PA levels (time walking, total time active, amount of steps) does not show a correlation with the FJS-12 and SQUASH, but does show a significant correlation with the HOOS-PS and PF-subscale of the SF-36 for which also sedentary time was correlated, though negatively as can be expected. The correlations found however were of moderate strength.

The SQUASH is a patient self-report of PA levels and thus is supposed to directly and most closely capture the dimensions assessed by the sensor-based PA. However, even for the same construct, the current study could not identify a correlation. Previous studies in orthopaedic populations investigating a correlation between the SQASH and objective PA measures from accelerometry could find some, mostly weak correlations. Patients after THA with unknown follow-up wore the ActiGraph accelerometer on a belt on the waist during a two-week period. Outcome, expressed in counts (the sum of accelerations measured during a time interval), was statistically significant correlated ($r_{spearman}$ 0.67, p = 0.01) with the total activity score of the SQUASH [29]. This was higher than found in the study by Wendel-Vos et al. who reported a Spearman correlation coefficient of 0.45 in healthy adults with the use of the Computer Science and Applications (CSA) Activity Monitor [24]. The ActiGraph generation used in these studies was a uniaxial accelerometer which is relative insensitive to PA that requires little vertical movements like cycling. In these studies, PA was not classified in activities but summarized in an intensity count related overall metric. The AM used in the current study does not have this limitation. Terwee et al. stated that a questionnaire assessing PA should be correlated to an accelerometer by at least 0.50 [30]. Unexpected, no correlations were found between the SQUASH and the time walked and total time active, not achieving the 0.50 limit stated by Terwee et al.

Analysis of AM parameters showed that the total time active, time walked and number of steps were all statistically significant positive correlated with the HOOS-PS. The HOOS-PS reports for PA during daily life, though not reporting for duration and frequency of PA as recommended by van Poppel et al., but by registering the prevalence and level of difficulties experienced during specific activities of daily life [26]. Apparently such difficulties experienced during descending stairs, getting in/out bath or shower, sitting, running and twisting/pivoting on a loaded leg are more

closely related with the ability of being active in daily life as represented by the total time active, time walked and number of steps performed. Nevertheless, the correlation is only moderate, which means that general and health related PA levels such as walking, daily steps taken and non-sedentary time are and can be achieved in THA patients with or without such self-reported difficulties. The investigation of such discrepancies may reveal valuable insights into THA patient outcomes and potential interventions beyond orthopaedics.

This study is the first in current literature correlating the FJS-12 with objectively measured PA. No correlations were found. The FJS-12 was designed to evaluate the patients' ability to forget about their operated joint in everyday life as a result of a successful arthroplasty. Subjects are asked for the awareness of an artificial joint during twelve different activities including physically demanding activities such as walking for more than 15 minutes, climbing stairs and when doing their favourite sport. In theory a high score and thus often forgotten joint during various activities shall facilitate and lead to higher and more intense PA in daily live. Subanalysis on the different questions was not performed, because the goal was to correlate the complete questionnaire with the objectively measured PA. The mean FJS-12 in the current study was low. Rosinsky et al. stated a threshold for success after THA with FJS-12 scores of 73.96 and 69.79 at 1- and 2-years follow-up respectively [31]. The current study reported the FJS-12 at almost 10-years follow-up and was highly influenced by three subjects with scores <5. In addition, a recent longitudinal study in TKA with a mean follow-up of 8.1 years (range 7.3 - 9.4) showed that PROMs and objective outcome measures drop over time [32]. Correlation testing also showed no statistically significant correlation between the FJS-12 and the SQUASH ($r_{pearson}$ .099, p = .616). It seems that daily life PA is not influenced by the degree of forgetting to have a hip replacement, both in self-report and objectively measured, but is influenced by other factors.

The present study does have limitations. At first, the SQUASH (91%) and FJS-12 (97%) were completed by a sufficient amount of subjects. However the analysis of the HOOS-PS was limited by a lower response and completion rate of 25 (78%) subjects submitting fully completed questionnaires, which seems more a limitation of the PROM itself. The 'running-difficulties' question was the main question not completed. Presumably because these subjects never tried to run and thus were not able to answer how much difficulty they experienced during running. Although one may think that 'extreme difficulties' is the appropriate answer for these subjects, the HOOS-PS requires five answers to calculate a total score. In comparison, in the current study the AM was worn for the appropriate 3 or 4 days by 88% of the subjects for a

mean 13.1 ± 1.8 hours per day and all data were available for analysis. PROMs remain inherently subjective, prone to an individual's interpretation and perception of joint functioning. Patients can have difficulties in keeping other negative conditions or illnesses out of consideration that might have impaired mobility, general condition or quality of life. The used PROMs don't take in to account for negative conditions or illnesses [33]. The fact that subjectively reported PA levels and objectively measured PA levels do not correlate may hint at the fact, that it is inherently difficult to recall in detail PA durations and frequencies without bias questioning this approach for individual or group outcome studies but limiting it maybe to large population based research where sensor-based assessment is not yet possible. A combination of PROMs and AM displays a patient's perception on physical functioning and the practitioner/researchers view on objectively determined PA of THA patients.

Conclusions

In conclusion, this study shows that PROMs are hardly affected by or do hardly capture levels and differences in objectively measured PA, a supposedly patient centred outcome and a goal of THA. Considering the value of PA for maintaining general health, and the restoration of PA via surgery such as THA, the value of using sensor based AMs to assess efficacy of treatments in this health related dimension or use it as a tool for patient education, awareness and communication, seems very high. Future studies should focus on the changes in health status as measured by PROMs and the correlation with objectively measured PA, for example pre and post total joint arthroplasty.

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5

Part B

Outcomes and Systemic Toxicity

Chapter VI

Outcome of Revised Metal-on-Metal Hip Arthroplasties: a Dutch Arthroplasty Register Study

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Je kunt beter ten onder gaan met je eigen visie dan met de visie van een ander

(Johan Cruijff)

Abstract

Background
Preliminary results of metal-on-metal (MoM) hip arthroplasty were satisfactory, but since 2004 data showed high failure rates. National joint replacement registries are multi-centre databases comprised of thousands of subjects and implants which allow for identifying variables predictive of implant failure. The aim of the current study was to estimate re-revision rates after revision of a primary MoM hip arthroplasty in the Dutch Arthroplasty Register (LROI) and to assess potential predictor variables of re-revision of these MoM hip arthroplasties.

Methods
Eligible procedures were those with a revision for any reason except infection, after an initial primary surgery with a hip resurfacing (HRA) or large-head MoM (LH-MoM) total hip arthroplasty (THA). The probability of re-revision for both types of MoM hip arthroplasty over time was estimated using the cumulative incidence function taking mortality as a competing risk into account. A proportional sub distribution hazards regression model was used to assess potential predictor variables of re-revision of these MoM hip arthroplasties.

Results
A total of 3476 records of revised implants were included, of which 873 (25.2%) were MoM-implants. Over the course of follow-up, 101 (11.5%) MoM implants were re-revised. During follow-up 36 (4.3%) patients who received a MoM-implant at primary arthroplasty and a revision afterwards had died. The regression model showed that for primary MoM-implants a MoM articulation after revision (HR 2.48; 95% CI 1.53 – 4.03, p<0.001), femoral-only revisions (HR 3.20; 95%CI 2.06– 4.99, p<0.001) and periprosthetic fractures (HR 1.98; 95% CI 1.03 – 3.82, p=0.042) as reason for the first revision were statistically significant risk-factors for re-revision.

Conclusion
Both types of large head MoM hip arthroplasties have shown high revision and re-revision rates, risk factors were identified. The outcome of this study can be helpful in managing expectations of patients and orthopaedic surgeons.

Introduction

Metal-on-metal (MoM) hip arthroplasty became a popular procedure during the 1990s for patients invalidated by osteoarthritis who demanded higher activity levels. Until then, a metal-on-polyethylene (MoP) hip arthroplasty was used with so-called conventional (not highly crosslinked) polyethylene, which wore out quickly and thus needed to be replaced or revised frequently [1]. Large head MoM (LH-MoM) total hip arthroplasty (THA) and hip resurfacing arthroplasty (HRA) have the advantage of low volumetric wear and high stability [2]. Preliminary results have been satisfactory and around 1.5 million procedures have been performed worldwide [3, 4]. Since 2004, multiple cohorts and national registry data showed high failure rates and the 10-year survival rate threshold of 95% set by The National Institute for Health and Care Excellence (NICE) was not achieved [5, 6]. The Dutch orthopaedic association (NOV) advised against the use of MoM-implants in 2012 [7, 8]. Revision procedures are commonly performed in patients with failed hip arthroplasties and in general are technically challenging and expensive procedures. Although these revisions provide clinical benefit and patient satisfaction, they tend to have a worse outcome when compared to primary THA procedures [9, 10]. Studies investigating the outcome of revision procedures are frequently limited by the small number of subjects included in these (single-centre) studies, hampering the detection of characteristics that could be a risk factor for revision [11-13]. National joint replacement registries are multi-centre databases comprised of thousands of subjects and implants which allow for identifying such variables of implant failure. The aim of the current study was to perform an exploratory approach to answer the research questions: 1) What is the re-revision rate after a first revision of a primary MoM hip arthroplasty, both HRA and LH-MoM THA? and 2) What are the risk factors for a re-revision after a primary MoM hip arthroplasty. To improve current practice, it is important to know the association between reason for first revision and the risk of re-revision. This should preferably lead to a better understanding of outcome in revision surgery.

Methods

Data sources
Data for the current study were provided by the Dutch Arthroplasty Register (LROI). This database is a nationwide population-based registry covering all hospitals in the Netherlands and was established by the NOV in 2007. At the time of the primary surgery both patient characteristics and surgical variables were recorded.

If applicable, the date of death according to the national insurance database on healthcare was linked to the data from the LROI via a trusted third party (ZorgTTP) to obtain mortality of registered patients [14]. All data in the LROI is collected in the context of improving quality of care. Therefore, the current study is not required to have an institutional review board approval. The study was conducted in accordance with the Good Clinical Practice-guidelines and performed in compliance with the 1975 Declaration of Helsinki, as revised in 2013.

Data selection

Revision procedures in patients with a history of primary LH-MoM THA (head diameter ≥36mm) or HRA until the end of the follow-up period on December 31st, 2018 were included. The primary surgeryshould have been performedbetween the start of the registry (2007) and January 1st 2012, when the ban by the NOV went into effect. In addition, we also selected data of all patients that received a first revision after an initial primary surgery with a non-MoM articulation in the same time period. All records with infection as a reason for the first revision were excluded (n=313, 8.9%).

The available patient characteristics were: sex, age at surgery (primary and revision), American Society of Anaesthesiologists (ASA) classification (primary and revision), indication for surgery (primary, revision and re-revision), previous surgery to the affected joint before the primary surgery, Body Mass Index (BMI; primary and revision) and smoking status (primary and revision; available from 2014). The available primary surgery characteristics were: type of surgery, year of surgery, surgical side and approach, type of implant, fixation, articulation and femoral head size. For revision and re-revision procedures the type and the reason for revision were studied, including the type of articulation after the first revision.

The dataset consisted of 2885 HRAs, 2670 LH-MoM THAs and 260874 non-MoM THAs. For the current study only the revised implant records were used. A total of 3476 revised implants records were included, of which 873 (25.1%) were MoM implants (in 839 patients) further subdivided into 545 (62.4%) LH-MoM THAs and 328 (37.6%) HRAs. The most common indication at primary surgery was osteoarthritis (89.1%). Baseline characteristics at first revision, of patients stratified to MoM and non-MoM implant, are shown in Table 1. More than one reason for revision could be registered; a total of 4253 reasons for 3476 procedures were found.

Statistics

Baseline characteristics and surgical variables of the cohort were stratified by type of bearing (non-MoM versus MoM) and described as absolute numbers (percentage) or as mean ± standard deviation (SD) [range]. Follow-up time was described as median and interquartile range (IQR). Differences in baseline characteristics between groups were tested using the independent-samples t-test and Pearson's chi-square test.

The probability of re-revision of MoM hip arthroplasty (HRA and LH-MoM THA) over time was estimated using the cumulative incidence function (CIF) taking mortality as a competing risk into account as both outcomes may not be completely uncorrelated. The CIF was chosen based on the current study goal 'to improve current practice, leading to better outcome in revision surgery'. The likely number of failures in practice are best represented by crude failure; composed by both failure of implants and mortality [15]. Cumulative incidence over time was visualised in a plot. The association between characteristics at the time of the first revision and the probability of re-revision was estimated using the proportional sub distribution hazards regression model and expressed as hazard ratio (HR) including the 95% confidence interval (CI), adjusted for age and sex [16]. BMI and Charnley classification were not recorded during the first years of the registry (<2014).

For this reason, it was chosen not to use these data but to use available cases for these associations as the percentage of missingness was high. Therefore, results for BMI and Charnley classification were considered preliminary. As the percentage of patients with bilateral implants was low (4.0%), no additional multilevel modelling to account for clustering of observations were performed. P-values ≤0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics 22 (International Business Machines Corporation, Armonk, New York, United States) and R version 3.6.1 (The R Foundation for Statistical Computing, Vienna University of Economics and Business, Vienna, Austria).

Table 1. Baseline characteristics of both patient groups at the time of the first revision procedure. P-values are given for differences between the groups.

	MoM implants	non-MoM implants	p-value
Number of subjects (%)	873 (25.1)	2603 (74.9)	
Age at surgery in years Mean ± SD [range]	62.1 ± 10.5 [20 – 89]	70.1 ± 11.0 [18 – 96]	<0.001*
FU[1] after primary surgery in years Median (IQR)	3.8 (2.1 – 5.8)	2.2 (0.5 – 5.3)	<0.001*
ASA-classification[2](%)			<0.001*
ASA I	271 (31.0)	400 (15.4)	
ASA II	462 (52.9)	1481(56.9)	
ASA III-IV	90 (10.3)	563 (21.6)	
Missing	50 (5.7)	159 (6.1)	
Smoking (%)			0.036*
Yes	53 (6.1)	103 (4.0)	
No	275 (31.5)	800 (30.7)	
Missing	545 (62.4)	1700 (65.3)	
BMI[3] (%)			
Underweight (BMI <18.5)	3 (0.3)	16 (0.6)	
Normal (BMI 18.5 – 25)	117 (13.4)	344 (13.2)	
Overweight (BMI 25 – 30)	144 (16.6)	384 (14.8)	
Obesity (BMI 30-40)	71 (8.1)	183 (7.0)	
Morbid obesity (BMI >40)	2 (0.2)	13 (0.5)	
Missing	10 (1.1)	27 (1.0)	
Not registrered before 2014	526 (60.3)	1636 (62.9)	

[1]Follow-up; [2]ASA: American Society of Anaesthesiologists; [3]BMI: Body mass index (kg/m^2); *P ≤0.05 significant. MoM: metal-on-metal. SD: standard deviation. IQR: interquartile range.

Results

The median follow-up time until the first revision for MoM implants was 3.8 years (IQR: 2.1 – 5.8 years), and for non-MoM implants 2.2 years (IQR: 0.5 – 5.3 years). The most common reason for revision in the MoM group was a 'symptomatic MoM-bearing' (43.1%), while for the non-MoM group these were 'dislocation or instability' (26.2%) and 'loosening of the femoral component' (21.5%) (Table 2). A total revision was performed far more often in the MoM-implant group: 45.8% vs 11.9% for the non-MoM implant group. Partial revisions after HRA were not common, in contrast to a cup revision (57.4% of revisions) for LH-MoM implants (Table 3). After the first

revision a polyethylene bearing was mostly used, either with a ceramic (40.8% and 29.5%), metal (24.6% and 50.6%) or zirconium (4.6% and 4.4%) femoral head, for the MoM and non-MoM group respectively.A MoM articulation was used in 12.9% of the revision cases of the primary MoM-implant group and only in 1.0% of the revision cases of the primary non-MoM implant group.

Over the course of follow-up, 101 (11.5%) MoM implants were re-revised. The median follow-up was 5.2 years (IQR: 2.2 – 7.3) after the first revision. During follow-up, 36 (4.3%) patients who received a MoM-implant at primary arthroplasty and a first revision surgery afterwards had died. In the non-MoM implant cohort, 367 (14.1%) re-revised implants were recorded at a median of 5.1 years follow-up (IQR:2.0 – 7.6). During follow-up 344 (13.3%) of 2589 patients had died after the first revision.

Figure 1 shows the cumulative incidence for the probability of re-revision over 10-years follow up with 95% confidence band, taking death as competing risk into account for MoM and non-MoM implants respectively. Beneath the figure the number of patients at risk at the start of each two-year interval is shown.

Table 2. Possible indications for first revision as documented in the Dutch Arthroplasty Register. Please note: more than one reason for revision could be registered.

	MoM implants (n=1145 indications)	**non-MoM implants (n=3106 indications)**
Indication	**Frequency (%)**	**Frequency (%)**
Dislocation	31 (2.7)	811 (26.2)
Girdlestone/spacer	6 (0.5)	52 (1.7)
Acetabular loosening	120 (10.5)	464 (15.0)
Femoral loosening	90 (7.8)	665 (21.5)
Periarticular ossification	8 (0.7)	58 (1.9)
Periprosthetic fracture	44 (3.9)	419 (13.5)
Insert wear	20 (1.7)	127 (4.1)
Symptomatic MoM bearing	494 (43.1)	10 (0.3)
Other	332 (28.9)	503 (16.2)

MoM: metal-on-metal.
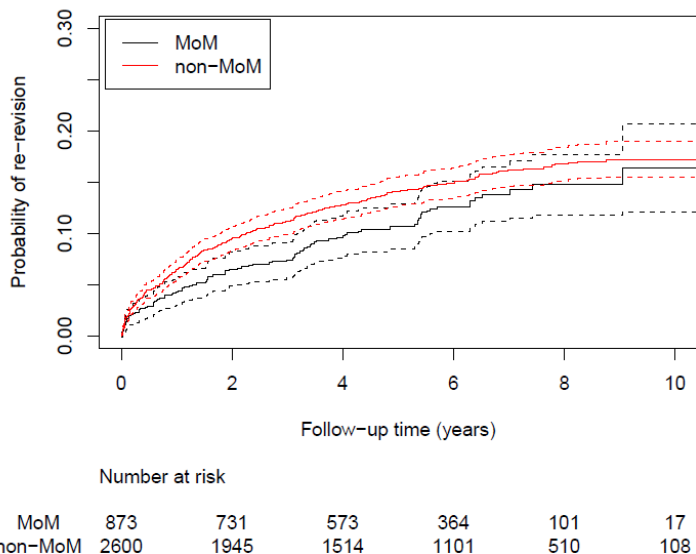
Figure 1. Competing risk analysis; cumulative incidencefor the probability of re-revision over 10-years follow up with 95% confidence band, taking death as competing risk into account for both groups of patients. Beneath the figure the number of patients at risk at the start of each two-year interval is shown.

Table 3. Type of first revision shown for each group of patients. Please note: more than one type could be registered.

Revision Type	MoM implants (n=873) Frequency (%)	HRA (n=328) Frequency (%)	LH-MoM (n=545) Frequency (%)	non-MoM implants (n=2603) Frequency (%)
Girdlestone	4 (0.5)	0 (0.0)	4 (0.7)	10 (0.4)
Partial: femoral head	423 (48.5)	36 (11.0)	387 (71)	2071 (79.6)
Partial: insert	281 (32.2)	8 (2.4)	273 (50.1)	989 (38)
Partial: cup	326 (37.3)	13 (4)	313 (57.4)	940 (36.1)
Partial: femur	75 (8.6)	29 (8.8)	46 (8.4)	858 (33)
Total revision	401 (45.8)	274 (83.5)	127 (23.3)	312 (11.9)
Other	3 (0.3)	0 (0.0)	3 (0.6)	15 (0.6)
Unknown	16 (1.8)	9 (2.7)	7 (1.3)	41 (1.6)

MoM: metal-on metal, HRA: hip resurfacing arthroplasty, LHMoM: large head MoM total hip arthroplasty

The proportional sub-distribution hazards regression model showed that revision to a MoM articulation after the first revision of a MoM-implant was a statistically significant risk-factor for re-revision (HR 2.48; 95% CI 1.53 – 4.03, $p<0.001$),

especially after revision of a LH-MoM THA (HR 3.45; 95% CI 1.89 – 6.30, p<0.001). Also, a periprosthetic fracture of a MoM-implant as reason for first revision was a statistically significant risk-factor for re-revision (HR 1.98; 95% CI 1.03 – 3.82, p=0.042). Most partial revisions of a MoM hip arthroplasty were statistically significant risk-factors for re-revision, especially femoral only revisions (HR 3.20, 95%CI 2.06 – 4.99, p<0.001). A symptomatic MoM bearing on the other hand was found as a statistically significant decreasing factor for the probability of re-revision (HR 0.53; 95% CI 0.35 – 0.82, p=0.004). The type of MoM-implant (resurfacing or LH-MoM THA) was not a statistically significant risk-factor for re-revision (HR 1.26; 95% CI 0.80 – 1.98, p=0.317). As comparison, associations computed on non-MoM implants are presented next to MoM-implants (Table 5).

Table 4. Type of articulation after the first revision shown for both groups of patients

Articulation after First revision	MoM implants (n=873) Frequency (%)	Non-MoM implants (n=2603) Frequency (%)
CoC	49 (5.6)	149 (5.7)
CoM	16 (1.8)	2 (0.1)
CoP	356 (40.7)	767 (29.5)
MoC	0 (0.0)	3 (0.1)
MoM	111 (12.7)	27 (1.0)
MoP	215 (24.6)	1316 (50.6)
ZoP	40 (4.6)	115 (4.4)
Unknown	2 (0.2)	3 (0.1)
Missing components (femoral head and/or inlay, and/or acetabulum)	84 (9.6)	221 (8.5)

*CoC ceramic-on-ceramic; CoM: ceramic-on metal; CoP: ceramic-on-polyethyelene; MoC: metal-on-ceramic; MoM: metal-on-metal; MoP: metal-on-polyethyelene; ZoP: zirconium-on-polyethyelene.

Discussion

The current study assessed the re-revision rate of MoM-implants (both HRA and LH-MoM THA) and possible risk factors forthese re-revision. The re-revision rate was shown to be 11.5% at a median follow-up of 5.2 years after the first revision. In comparison, the re-revision rate of non-MoM THA was shown to be 14.1% at 5.1 years follow-up. A MoM-articulation post-first-revision, a periprosthetic fracture as reason for first revision and femoral-only revisions were found as statistically significant risk factors for re-revision in MoM-implants.

Table 5. Risk factors and their hazard-ratio and level of significance (p-value) for re-revision shown for all groups of patients, adjusted for age and sex.

Variable	MoM implants		HRA		LHMoM		Non-MoM implants	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
BMI[1]	0.99 (0.89 – 1.10)	0.890	1.00 (0.85 – 1.18)	0.964	0.99 (0.87 – 1.15)	1.000	1.03 (0.99 – 1.07)	0.110
ASA-classification[2,‡]								
I/II	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
(III/IV)	0.68 (0.29 – 1.61)	0.382	2.18 (0.63 – 7.57)	0.221	0.43 (0.13 – 1.43)	0.169	1.17 (0.90 – 1.52)	0.248
Primary implant type								
LH-MoM	1.00	1.00	NA	NA	NA	NA	NA	NA
Resurfacing	1.26 (0.80 – 1.98)	0.317	NA	NA	NA	NA	NA	NA
Reason for first revision								
Dislocation	1.33 (0.52 – 3.39)	0.551	un	un	2.25 (0.86 – 5.90)	0.09	1.18 (0.95 – 1.47)	0.125
Girdlestone /spacer	1.74 (0.23 – 13.39)	0.593	un	un	2.80 (0.33 – 24.15)	0.349	1.13 (0.57 – 2.23)	0.724
Acetabularloosening	1.00 (0.57 – 1.74)	0.991	0.93 (0.39 – 2.23)	0.875	1.05 (0.50 – 2.22)	0.901	0.98 (0.75 – 1.30)	0.902
Femoralloosening	1.51 (0.88 – 2.60)	0.138	1.05 (0.46 – 2.40)	0.914	2.20 (1.05 – 4.60)	0.036*	0.93 (0.74 – 1.19)	0.574
Periarticularossification	0.83 (0.11 – 6.01)	0.850	0.86 (0.11 – 6.53)	0.882	un	un	0.95 (0.49 – 1.87)	0.889
Periprostheticfracture	1.98 (1.03 – 3.82)	0.042*	2.17 (0.90 – 5.25)	0.086	1.76 (0.64 – 4.86)	0.274	0.77 (0.60 – 1.06)	0.113
Insertwear	1.99 (0.66 – 6.01)	0.220	2.88 (0.88 – 9.50)	0.082	1.22 (0.16 – 9.35)	0.850	0.76 (0.39 – 1.49)	0.424
SymptomaticMoMbearing	0.53 (0.35 – 0.82)	0.004*	0.79 (0.42 – 1.51)	0.481	0.41 (0.23 – 0.73)	0.002*	NA	NA
Articulation after first revision[3]								
CoP/MoP/ZoP	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MoM	2.48 (1.53 – 4.03)	<0.001*	1.90 (0.85 – 4.26)	0.117	3.45 (1.89 – 6.30)	<0.001*	1.12 (0.51 – 2.48)	0.780
CoC	0.78 (0.28 – 2.18)	0.644	0.73 (0.22 – 2.46)	0.613	1.18 (0.16 – 8.95)	0.875	0.55 (0.33 – 0.93)	0.026*
CoM/MoC	un	un	un	un	un	un	1.22 (0.23 – 6.50)	0.820

Type of first revision								
Partial: femoral head	1.21 (0.82– 1.79)	0.339	2.83 (1.48 – 5.40)	0.002*	0.97 (0.53 – 1.78)	0.930	0.96 (0.75 – 1.23)	0.753
Partial: insert	0.55 (0.33– 0.90)	0.017*	1.88 (0.39 – 8.99)	0.427	0.47 (0.27 – 0.83)	0.009*	0.85 (0.68– 1.06)	0.141
Partial: cup	0.65 (0.42– 1.01)	0.054	0.39 (0.05 – 2.96)	0.363	0.63 (0.37 – 1.10)	0.104	0.84 (0.86– 1.05)	0.134
Partial: femur	3.20 (2.06– 4.99)	<0.001*	3.62 (1.88 – 6.96)	<0.001*	3.19 (1.70 – 6.00)	<0001*	0.82 (0.65– 1.03)	0.082
Total revision	0.64 (0.42– 0.97)	0.036*	0.31 (0.17 – 0.58)	<0.001*	0.73 (0.35 – 1.51)	0.394	0.85 (0.61– 1.20)	0.359

[1]BMI: Body mass index (kg/m²); ‡based on available cases, [2]ASA: American Society of Anesthesiologists; NA: not applicable, un: unable to estimate due to too few observations;[3] CoP: ceramic-on-polyethylene; MoP: metal-on-polyethylene; ZoP: zirconium-on-polyethyelene; MoM: metal-on-metal; CoC ceramic-on-ceramic; CoM: ceramic-on metal; MoC: metal-on-ceramic, *P ≤0.05 significant, HR: hazard ratio

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Wong et al. used the Australian registry and showed that 884 (5.8%) out of 15360 HRA subjects underwent revision for another reason than infection. Another 102 (11.5%) subjects underwent re-revision, which resulted in a cumulative percent re-revision of 26% at 10-years (95%CI 19.6–33.5). No differences in survivorship were found for the type of revision or bearing surface used during revision surgery. Other variables such as patient characteristics (e.g. BMI) and surgical techniques (e.g. surgical approach, type of implant) were not investigated [17]. In contrast, the current study combined both types of MoM hip arthroplasties (HRA &LH-MoM THA). Type of MoM implant was not a risk factor for re-revision in the current study. In earlier studies, BMI, cobalt-chromium-containing bearing surfaces after first revision, soft tissue damage and pseudotumor/adverse reactions to metal debris (ARMD) as the reason for the first revision were shown to be variables prognostic for a poor outcome after the revision of a LH-MoM THA [13, 18]. The current study added new proof to chromium-containing bearing surfaces (MoM) after first revision as risk-factor for re-revision.

A symptomatic MoM bearing as the reason for the first revision was found not to be a risk factor for re-revision. Matharu et al. showed that re-revision was performed in 192 (7.6%) of 2535 subjects after a first revision for ARMD in subjects with a HRA or LH-MoM THA. This is lower than the re-revision rate for any reason found in the current study. They found a high BMI at first revision, modular component-only revisions (head and insert with or without taper adapter), ceramic-on-ceramic revision bearings and acetabular bone grafting as predictors of re-revision [19]. Bonner et al. reported that complications after the first revision (dislocation, ARMD, fracture, loosening and infection) were risk-factors for re-revision and also the use of a metal femoral head placed at the time of first revision compared to a ceramic femoral head, both with a polyethylene liner. In contrast to Matharu et al., BMI was not found to be a statistically significant risk factor [12]. In accordance, Lainiala et al. reported re-revision rates of 7.0% after a first revision because of ARMD in 528 MoM hip arthroplasties. Dislocation was the most common reason for re-revision, in both uni-, and multivariable analysis, a first revision head size of ≤36mm was associated with an increased risk for dislocation [20].

The strengths of the current study are the high coverage (100%) and completeness of the LROI database: 98-99% for primary THAs and 88-97% for hip revision arthroplasties between 2012 and 2019, the relatively large sample size, high diversity of hospitals, surgeons, patients and prostheses and thus a high generalizability. However, there are alsosome limitations of the current study. In the first years, starting in 2007, the completeness of LROI-data was not optimal with 88% in 2009, but raised to >95% in the years after [21,22]. Also, specification of ARMD and high metal ion concentrations as reason for revision is not available as a possible reason for revision. These are

combined as 'symptomatic MoM bearing'. Patient surveillance was promoted in the last decade and the threshold to perform revision surgery was lowered by surgeons and worldwide regulatory authorities [23]. The destructive nature of ARMD makes hip stability and poor bone stock essential in revision surgery [24]. In addition, the current study found periprosthetic fractures in MoM-implants as risk factor for re-revision. We selected LROI-data of patients who underwent a first revision of their hip arthroplasty due to any reason, except infections. Patients who were treated with a plate osteosynthesis, without a revision of one or more implant components (cup, insert or stem) in case of a periprosthetic fracture, are not registered. HRA and LH-MoM THA were frequently used during the first years of the register. Despite the high revision and re-revision percentage of MoM hip arthroplasties, the absolute number of re-revisions was low. Therefore, a Type II error may be present. Patient selection for (un)cemented THA (MoM and non-MoM) and HRA is influenced by age and sex, as was observed, but also by general health and functional demands potentially influencing the outcome. Implant survival or -failure can be estimated with the present data, but functional outcome including non-surgical complications and non-revised surgeries (e.g. debridement because of early infection) are unknown. Large numbers of implant records can give rise to small p-values and narrow confidence intervals, but the statistically significant findings may not always be of clinical relevance. National arthroplasty registry studies are limited by compliance of health institutions (at least 80%), completeness (at least ≥90%) and revision surgery as the only outcome criteria [26]. The LROI meets these requirements with a coverage of 100% and a completeness >95% [21,22].

In conclusion, the current study aimed to answer what the re-revision rate after a first revision of a primary MoM hip arthroplasty is, and what risk factors for a re-revision after a primary MoM hip arthroplasty exist. MoM hip arthroplasties, both HRA and LH-MoM THA, have shown high revision and re-revision rates. These re-revision rates are comparable and even less frequent when compared to non-MoM arthroplasty. In accordance, also the mortality rate in MoM arthroplasty was lower, possibly because MoM arthroplasty was more frequently used in young and healthy patients (ASA I). Early revision for a symptomatic MoM bearing was found as a protective factor for re-revision. This indicates a decent surgical experience in The Netherlands for this type of revisions, potentially contributed by patient characteristics such as minimal bone loss and a good bone stock, in combination with the specific aspects of patients selected for MoM bearings (young and active). Femoral-only revisions and MoM articulations post-revision should not be used during the first revision of a failed MoM hip arthroplasty. The outcomes of this study can be helpful in managing expectations of patients and orthopaedic surgeons.

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Chapter VII

Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports

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One man can be a crucial ingredient on a team,
but one man cannot make a team
(Kareem Abdul-Jabbar)

Abstract

Introduction
Prosthetic Hip-Associated Cobalt Toxicity (PHACT) is caused by elevated blood cobalt concentrations after hip arthroplasty. This systematic review aims to determine which symptoms are reported most frequently and in what type of bearing. We also try to determine the blood level of cobalt concentrations associated with toxicological symptoms.

Methods
A systematic review was conducted on the 10th of July according to PRISMA guidelines. A methodological quality assessment (Risk of bias; RoB) was performed. Primary outcomes were the reported symptoms of cobalt toxicity and the level of cobalt concentrations in blood. These levels were associated with toxicological symptoms. A total of 7645 references were found of which 67 relevant reports describing 79 patients.

Results
The two most used bearings in which prosthetic hip-associated cobalt toxicity was described were metal-on-metal (MoM) bearings (38 cases) and revised (fractured) ceramic-on-ceramic (CoC) bearings where the former ceramic head was replaced by a metal head (32 cases). Of all reported symptoms, most were seen in the neurological system, of which 24% were in the sensory system and 19.3% in central/peripheral system, followed by the cardiovascular (22.1%) system. The mean blood cobalt concentration on which the symptoms were presented was 572 ± 962.2 ppb in the entire cohort. The mean cobalt concentration for MoM-bearings was 123.7 ± 96.8 ppb and 1078.2 ± 1267.5 ppb for the revised fractured CoC-bearings.

Discussion
Prosthetic hip-associated cobalt toxicity might occur after primary MoM- and revised fractured CoC-bearings. Sensory, neurological and cardiovascular symptoms were most reportedly most frequently in relation to elevated cobalt concentrations.

Introduction

Exposure of metal ions after hip arthroplasty surgery is a widely reported phenomenon. Multiple studies have shown that increased metal ions can result in local soft tissue reactions, described as Adverse Reaction to Metal Debris (ARMD) [1-4]. There is, also an increasing number of case reports describing systemic reactions in relation to elevated blood cobalt concentrations, known as Prosthetic Hip-Associated Cobalt Toxicity (PHACT)[5, 6].

Increased cobalt concentrations are often seen after implantation of metal-on-metal (MoM) hip-bearings [7]. This can be due to the release of ions from the metal (cobalt-chromium) surface either directly (corrosion) or during sliding under load, which may create wear particles (adhesion). Another source of significant metal particle release is the application of a metal component for revision of a fractured ceramic head and/or a fractured ceramic acetabular liner. In this scenario, massive three-body abrasive wear can be created, as small remaining particles of the fractured ceramic bearing lead to abrasion of the metal surface [8, 9].

The systemic effects of cobalt toxicity are historically well documented from industrial exposure, iatrogenic use of oral cobalt chloride tablets and from the beer industry as foam stabilizing agent [10-12]. The toxicity of cobalt is related to the unbound (free) form of cobalt (Co^{2+}) and certain patient conditions. Unice et al. stated that kidney failure, iron deficiencies, sepsis, malnutrition and use of certain medication increased the toxicity of cobalt at lower concentrations [13]. The systemic complaints in patients with PHACT may lead to a variety of symptoms: neuro-ocular toxicity (e.g. tinnitus, vertigo, deafness, blindness, convulsions, headaches and peripheral neuropathy), cardiotoxicity and thyroid toxicity [14]. Nausea, anorexia and unexplained weight loss have also been described [6, 15-17]. Initially there were concerns that high cobalt and chromium concentrations increased the risk of cancer; however this was not proven in large comparative studies [18, 19].

It is still unknown which of these systemic symptoms are mostly reported in PHACT and at what blood cobalt concentration toxicity occurs. The present study is a systematic review of the current literature reporting systemic cobalt toxicity symptoms after any type of hip arthroplasty. The aim is to define and present the most reported systemic symptoms related to PHACT and to determine blood cobalt levels associated with toxicity.

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Methods

The study protocol of this systematic review on case-reports was registered in PROSPERO, the international prospective register of systematic review, with registration number: CRD42020215827.

Criteria for considering studies for this review

Types of studies and participants

Case reports concerning cobalt toxicity after hip arthroplasty were included. Patients with any type of bearing (MoM, CoC, metal-on-polyethylene (MoP), ceramic-on-polyethylene (CoP)) and any type of hip arthroplasty design (hip resurfacing arthroplasty (HRA), short stem hip arthroplasty, 'conventional' stemmed total hip arthroplasty, both uncemented and cemented) were included. Articles describing allergic reactions on hip prosthesis and/or cobalt, and articles reporting only local problems around the hip such as Adverse Local Tissue Reactions (ALTR), ARMD and Aseptic Lymphocytic Vasculitis-Associated Lesion (ALVAL) were excluded.

Types of interventions

The description of an intervention was not necessary for inclusion, as patients may have died from cobalt toxicity before an intervention could be initiated. In some cases, a revision arthroplasty or chelation therapy was the intervention of choice of the attending physicians.

Types of outcome measures

Primary outcomes were the reported symptoms of cobalt toxicity and the blood cobalt concentration at which these symptoms were seen. All reported symptoms were counted and divided into nine different categories, based on the physiological system related to the occurrence of the symptoms. We followed the categories used in the study of Devlin et al., with some minor adjustments [6]. Cobalt concentrations in blood were reported in nmol/L, µg/L and parts per billion (ppb). Cobalt concentrations in nmol/L were converted to ppb whereas 1 nmol/L = 0.059 ppb.

Search methods for identification of studies

The search was performed on July 10, 2020 in PubMed, EMBASE, Cochrane Library/ Wiley, CINAHL (EBSCO), Web of Science (Clarivate Analytics) and Trial registers (PROSPERO) by one author (MH). The following [MESH] search terms were used: "Hip Prosthesis, Arthroplasty, Replacement, Hip and Cobalt. The full search strategy and terms can be found in Appendix 3. Articles published in Dutch, English, German or Spanish were included. There were no further restrictions for publication type

or date. Reference lists of included articles were screened for missing items. In addition, also posters presented at congresses and published abstracts were included. Duplicates were identified by one author (JJ) in RefWorks. All records were independently screened on title and abstract by two authors (JJ, MS), disagreement was resolved by mutual discussion. Full-text articles were assessed for eligibility by two authors (JC, MK), differences were resolved in a consensus meeting and if necessary, through discussion with another author (JJ).

Data collection and analysis

Two authors (JC, MK) independently extracted data of the included articles and obtained the degree of bias. Differences were resolved through discussion with another author (JJ). Data were extracted and stored in a Microsoft Excel 2019 file (Microsoft, Redmond, Washington, United States). The following data of the included studies was extracted: study ID (author, year of online publication), number of patients (N), patient characteristics at onset of symptoms (age in years, sex), primary intervention and indication for the primary procedure, secondary intervention and indication (if applicable), follow-up (in months) since surgery, cobalt ion concentration in any type of amount (e.g. nmol/L, μg/L, ppb) when symptoms were seen, symptoms reported, outcome after treatment, regardless of the type of treatment. All results are presented as total (percentage) or as mean (standard deviation).

Quality assessment

The risk of bias (RoB) tool of the Cochrane Handbook for Systematic Reviews of Interventions was used and the Newcastle-Ottawa Scale (NOS) was chosen to assess the quality of the articles [20-22]. This checklist is used to determine quality of non-randomized studies, including case-controlled and cohort studies, in three areas: selection, comparability and the ascertainment of either the exposure or outcome of interest. An assessment scale is available to award stars with a maximum score of 9: one for each question in the selection and outcome scale, and two for the comparability domain (appendix 1) [21]. The follow-up as described in question 6 was determined to be at least three months in agreement with all authors. A score of less than 5 stars represents a high RoB [23].

In addition, a checklist suggested by Murad et al. was also used to obtain RoB [24]. This checklist is especially designed for case reports and exists of an eight-item tool categorized in four domains: selection, ascertainment, causality and reporting. It is a modification of the tools by Pierson, Bradford Hills and the NOS (appendix 2)[24]. The eight items of the tool were scored yes or no. Like the NOS, the adequate follow-up was determined to be three months. Questions 5 and 6 of the questionnaire

were not taken into account since they were mostly relevant to cases of adverse drug events. Quality of the articles was defined 'good' when ≥4 times were scored 'yes', 3-2 times 'yes' was defined 'moderate' and ≤1 time 'yes' as 'poor'. All eligible case reports were included in the review irrespective of their methodological quality.

Results

Our search identified 7645 references of which 3898 were screened after removal of duplicates (appendix 3). A total of 3824 were excluded based on title or abstract, resulting in 74 eligible articles. Of these, a total of 67 were included for analysis after excluding another 7 studies, due to no original case description, retraction and no described toxicity (Figure 1). The RoB classification according to the NOS checklist resulted in a 98.5% (N = 66) of low risk of bias and 1.5% (N = 1) of high-risk bias of the case reports (see appendix 4). According to the checklist of Murad et al., 76.1% (N = 51) of the studies were classified as good methodological quality. A full review of the Murad checklist is found in appendix 5.

We identified a total of 79 patients with reported PHACT. Table 1 presents the most important data of all articles and methodological quality assessment score. The full overview is shown in appendix 6. A total of 46 (58.2%) patients were male and 27 (34.2%) were female. Sex was not mentioned in 6 patients. The mean age at primary surgery was 53.2 ± 14.2 years. The main known reason for primary surgery was osteoarthritis (N=28; 35.4%), however, in most reports the primary indication was unknown (N=36; 45.6%). Table 2 presents the demographic data of the entire group.

PHACT related to type of bearing
The two most used bearings in the primary surgery were MoM (N=38; 48.0%) and CoC (N=32; 40.5%). Also MoP (N=2; 2.5%) and CoP (N=2; 2.5%) were reported, in 5 cases (6.5%) no primary bearing was reported.

In 38 (48.0%) patients the PHACT symptoms occurred after primary surgery of which in 34 (89.5%) after a primary MoM-bearing. The mean time between the primary surgery and onset of symptoms was 2.1 (range: 0-13) years. A total of 41 (52.0%) patients developed PHACT symptoms after they had revision surgery. Especially revision of a (fractured) CoC-bearing for a MoP- (N = 21) or MoM-bearing (N = 6) caused the onset of cobalt toxicity symptoms. In this group the mean time of developing PHACT was 8.8 (range: 4-15) years after the primary surgery, and 2.4 (range: 0-9) years after the revision surgery (table 3).

Table 1. Most important details of the reviewed articles and quality assessment score results. For a complete overview see appendix 2.

Author (year)	No of patients	Major Reported Systemic Symptoms (classified)	Cobalt in ppb (sample)	Primary intervention	Secondary intervention	Indication revision	Quality score NOS	Murad
Allen (2014)[32]	1	Cardiovascular	287.6 (S)	MoM	CoP	Systemic symptoms	Low	Good
Apel (2013)[33]	1	Neurological (Sensory and C/P) Cardiovascular	355 (S)	CoC	MoC	Fracture CoC implant	Low	Good
Austin (2015)[34]	1	Neurological (Sensory) Cardiovascular	1351.4 (WB)	-	-	Systemic symptoms	Low	Good
Balbouzis (2016)[35]	1	Cardiovascular	22.2 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Bartholomeu (2018)[36]	1	Neurological (Sensory)	-	-	-	Systemic symptoms	Low	Good
Biglia (2020)[37]	1	Mental/Psychosocial	14 (WB)	CoC	MoM	Fracture CoC implant	Low	Good
Bonilla (2018)[38]	1	Cardiovascular (shock)	100 (WB)		-	Systemic symptoms	Low	Good
Briani (2015)[39]	1	Neurological (C/P)	14.3 (WB)	CoC	-	Systemic symptoms	Low	Good
Charette (2017)[40]	1	Cardiovascular	156 (S)	MoM bilateral	CoP	Systemic symptoms	Low	Good
Choi (2019)[41]	2	Cardiovascular Neurological (Sensory)	489.5 (S)	CoP	MoP	Fracture CoC implant	Low	Good
		Cardiovascular	111.9 (S)	CoC bilateral	CoM	Fracture CoC implant		
Citak (2018)[42]	1	Cardiovascular Neurological (Sensory)	-	CoC	MoP	Fracture CoC implant	Low	Poor
Czekaj (2013)[43]	1	Neurological (Sensory and C/P)	206 (WB)	MoM	CoP	Systemic symptoms	Low	Good
Dahms (2014)[44]	1	Neurological (Sensory) Cardiovascular	885 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Davies (2019)[45]	1	Neurological (Sensory) Cardiovascular	953 (S)	CoC	MoP	Fracture CoC implant	Low	Poor
Dolliana (2016)[46]	1	Neurological (Sensory) Gastroenterology	819.2 (WB)	CoC	MoM	Fracture CoC implant	Low	Moderate
Enseleit (2016)[47]	1	Neurological (Sensory) Cardiovascular	-	Bilateral	-	Systemic symptoms	Low	Poor
Esteban Sánchez (2016) [48]	1	Neurological (Sensory and C/P) Cardiovascular	1036 (S)	CoC	MoP	Fracture CoC implant	Low	Good

Study		Symptoms					Risk	Quality
Fox (2016)[29]	1	Neurological (Sensory and C/P) Cardiovascular	817 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Garcia (2020)[49]	1	Neurological (Sensory and C/P) Cardiovascular	1000 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Gautam (2019)[50]	1	Cardiovascular	373 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Giampreti (2014)[51]	1	Neurological (C/P)	352.6 (S)	MoM	CoP	Hip pain	Low	Moderate
Giampreti (poster, 2014) [52]	4	Neurological (Sensory and C/P) Cardiovascular	50 (WB) 352.6 (WB) 201.3 (WB) 201.3 (WB)	MoM MoM MoM MoM	- - - -	Systemic symptoms Systemic symptoms Systemic symptoms Systemic symptoms	Low	Moderate
Gilbert (2013)[53]	1	Cardiovascular	1085 (S)	CoC bilateral	MoP	Fracture CoC implant	Low	Good
Goel (2016)[54]	1	Cardiovascular (shock)	25 (S)	MoM bilateral	-	Systemic symptoms	Low	Moderate
Grant (2016)[55]	1	Neurological (Sensory and C/P)	2148(P)	CoC	MoM	Fracture CoC implant	Low	Good
Griffiths (2015)[56]	1	Neurological (Sensory and C/P) Cardiovascular	2006 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Grillo (2016)[57]	1	Neurological (Sensory) Cardiovascular	107.8 (S)	CoC	MoM	Fracture CoC implant	Low	Good
Grosso (2018)[58]	1	Neurological (Sensory)	1076 (WB)	CoC	MoM	Fracture CoC implant	Low	Poor
Guevara (2018)[59]	1	Neurological (Sensory) Cardiovascular	-	-	-	Systemic symptoms	Low	Poor
Harris (2015)[60]	1	Neurological (Sensory and C/P) Cardiovascular	788.1 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Ho (2018)[61]	1	Neurological (Sensory and C/P) Cardiovascular	799 (S)	CoC	-	Systemic symptoms	Low	Moderate
Ikeda (2010)[62]	1	Neurological (C/P)	400 (WB)	CoC bilateral	MoP	Fracture CoC implant	Low	Good

Study	N	Type	Value	Implant	Bearing	Complication	Risk	Quality
Jones (1975)[25]	7	Not classified		McKee hip	Girdlestone	Recurrent dislocations	Low	Good
		Not classified		McKee hip	MoP	Possible fracture		
		Not classified		McKee hip	MoP	Persistent pain		
		Skin/hair		McKee hip bilateral	Girdlestone	Protrusion acetabulum		
		Not classified		McKee hip	None described	Hip pain		
		Not classified		McKee hip	Recemented prosthesis	-		
		Not classified		McKee hip	MoP	Recurrent dislocations		
Kao (poster, 2014)[63]	1	Neurological (C/P)	20 (WB)	Bilateral MoP	-	Systemic symptoms	Low	Moderate
Kim (2016)[64]	1	Neurological (Sensory and C/P) Cardiovascular	397.8 (WB)	CoP bilateral	MoP	Fracture CoP implant	Low	Good
Lapena Motilva (2019)[65]	1	Neurological (Sensory and C/P)	892.8 (WB)	-	-	Systemic symptoms	Low	Good
Lecoanet (2019)[66]	1	Neurological (Sensory and C/P) Cardiovascular	1463.7 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Leikin (2015)[67]	1	Neurological (Sensory and C/P)	1096.5 (S)	CoC	MoM	Fracture CoC implant	Low	Poor
Machado (2012)[68]	1	Cardiovascular	13.6 (P)	MoM	-	Systemic symptoms	Low	Poor
Mao (2011)[69]	2	Neurological (Sensory and C/P)	24.2 (S)	MoM	CoP	Systemic symptoms	Low	Good
		Neurological (Sensory and C/P)	15.2 (S)	MoM	CoP	Systemic symptoms		
Marcus (2014)[70]	1	Neurological (Sensory and C/P)	-	MoM	MoP	Systemic symptoms	Low	Moderate
Martin (2015)[71]	1	Cardiovascular	192 (S)	MoM bilateral	Bilateral CoP	Systemic symptoms	Low	Good
Moniz (2017)[72]	1	Cardiovascular	169 (S)	MoM	CoP	Systemic symptoms	Low	Good
Mosier (2016)[73]	1	Cardiovascular	189 (S)	MoM bilateral	Dual Mobility CoP	Systemic symptoms	Low	Good
Ng (2013)[74]	1	Neurological (Sensory and C/P)	44.7 (S)	MoM bilateral	-	Systemic symptoms	Low	Good
Nogar (2018)[75]	1	Neurological (C/P) Cardiovascular	208 (S)	MoM	-	Systemic symptoms	Low	Good

Study	n	System affected	Metal level	Bearing	Bearing 2	Indication	NOS	Quality
Oldenburg (2009)[26]	1	Neurological (Sensory and C/P) Cardiovascular	625 (S)	CoP	MoP	Fracture CoP implant	Low	Good
Payen (2015)[76]	1	Cardiovascular (shock)	267.2 (WB)	MoM bilateral	-	Systemic symptoms	Low	Good
Pelayo-de Tomas (2017)[77]	1	Neurological (Sensory and C/P) Cardiovascular	651.2 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Pelclova (2012)[78]	1	Neurological (Sensory and C/P)	506 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Peters (2017)[79]	1	Neurological (Sensory and C/P)	596.5 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Reich (2019)[80]	1	Neurological (C/P)	10.1 (S)	Revision MoM	2nd revision MoP	Acetabular osteolysis	Low	Good
Reid (2014)[81]	1	Cardiovascular	-	MoM	Unstable	Systemic symptoms	Low	Good
Rizzetti (2009)[27]	1	Neurological (Sensory and C/P)	549 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Sanchez Dalmau (2015)[82]	1	Neurological (Sensory and C/P)	259 (P)	MoP bilateral	Chelation therapy	Systemic symptoms	High	Poor
Sanz Perez (2019)[83]	1	Cardiovascular (shock)	652 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Shapiro (2018)[84]	1	Neurological (C/P)	39 (S)	MoM	CoP	Systemic symptoms	Low	Good
Sotos (2013)[85]	1	Neurological (Sensory and C/P)	122 (S)	MoM	CoP	Systemic symptoms	Low	Good
Steens (2006)[28]	1	Neurological (Sensory and C/P)	-	CoC	CoM	Chronic pain	Low	Good
Tilney (2017)[86]	1	Cardiovascular	246.3 (WB)	MoM	-	Systemic symptoms	Low	Good
Tower (2012)[87]	1	Neurological (Sensory and C/P)	74 (S)	MoM	-	Systemic symptoms	Low	Poor
Tower (2010)[88]	2	Neurological (Sensory and C/P) Cardiovascular	122 (S) / 23 (S)	MoM / MoM	- / -	Systemic symptoms / Systemic symptoms	Low	Good
Vasukutty (2016)[89]	1	Cardiovascular	44.9 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Woelber (2016)[90]	1	Neurological (Sensory and C/P)	116 (S)	MoM bilateral	Bilateral CoP	Systemic symptoms	Low	Good
Wong (2014)[91]	1	Skin/hair	57.1 (S)	MoM	ToP	Systemic symptoms	Low	Good
Zeynalov (2018)[92]	1	Mental/Psychosocial	1.6 (S)	MoM	CoM	Systemic symptoms	Low	Good
Zywiel (2013)[93]	1	Cardiovascular	6521 (WB)	CoC	MoP	Fracture CoC implant	Low	Good

No: number, C/P: central and peripheral, ppb: parts per billion, S: serum, WB: whole blood, P: plasma, NOS: Newcastle-Ottawa Scale, MoM: Metal-on-Metal, CoC: Ceramic-on-Ceramic, CoP: Ceramic-on-Polyethylene, MoP: Metal-on-Polyethylene, ToP: Titanium-on-Polyethylene
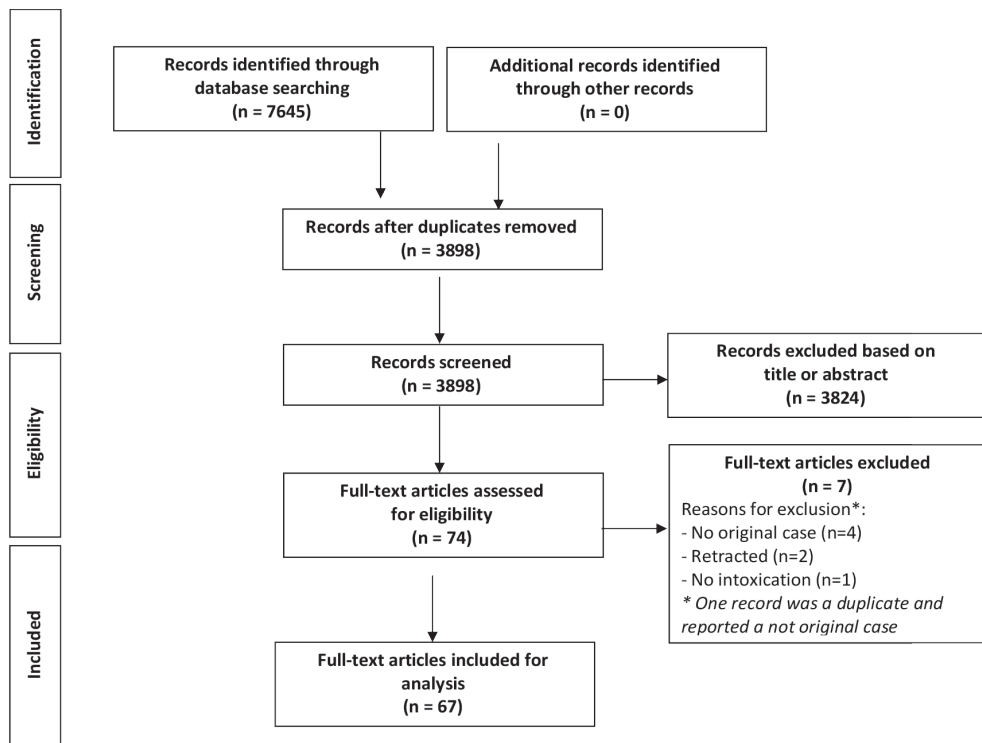
Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart

PHACT related systemic symptoms

A total of 321 symptoms were scored and divided into nine different categories; neurological, cardiovascular, gastroenterology, musculoskeletal, skin/hair, thyroid, mental/psychosocial and others. The neurological symptoms were subcategorized in central/peripheral and sensory. Some patients had more than one reported symptom during the first presentation. All documented symptoms were considered and scored as possible PHACT. Table 4 shows all the different symptoms in the nine different categories.

The most identified symptoms were neurological related. Since most symptoms were especially related to the sensory system, we divided them into sensory system (N=77; 24.0%) and central/peripheral (N=62; 19.3%) related symptoms.

Hearing impairment/loss and visual impairment/retinal dysfunction were the most mentioned problems in the sensory system, with a total of 34 (44.2%) and 25 (32.5%) respectively. Within the 79 described patients, hearing impairment/loss encounters

for a total of 43.0% and visual impairment/retinal dysfunction for 31.6%. In the central/peripheral group the most described symptoms were cognitive, memory, or concentration problems (N=16;12.6%) and paraesthesia/anaesthesia (N=13; 16.5%).

Table 2. Demographics of all patients (n=79)

Variable	Total
Primary surgery	
Mean age at primary surgery (SD)	53.2 (14.2)
Indications for primary surgery (%)	
Primary osteoarthritis	28 (35.4)
Avascular necrosis	9 (11.4)
Fracture	3 (3.8)
Dysplasia	2 (2.5)
Hip pain	1 (1.3)
Unknown	36 (45.6)
Male/Female (%)	46/27 (58.2 / 34.2)
Primary bearing (%)	
MoM	38 (48)
CoC	32 (40.5)
MoP	2 (2.5)
CoP	2 (2.5)
Unknown	5 (6.5)
Revision surgery	
Mean age at revision surgery (SD)	58.6 (11.1)
Indication for revision surgery (%)	
Systemic symptoms	38 (48.1)
Fracture CoC	31 (39.2)
(chronic) Pain	4 (5.1%)
Recurrent dislocations	2 (2.5%)
Protrusion acetabulum	1 (1.3%)
Fracture	1 (1.3%)
Osteolysis	1 (1.3%)
Unknown	1 (1.3%)
Male/Female (%)	26/15 (63.4 / 36.6)
Cobalt toxicity	
Mean age at onset of symptoms	59.0 (11.5)
Primary PHACT complaints (%)	38 (48)
Revision PHACT complaints (%)	41 (52)
Mean cobalt toxicity level in ppb (SD)	572 (962.1)
Mean follow up time in months (SD)	12.7 (14.2)

SD: standard deviation, MoM: Metal-on-Metal, CoC: Ceramic-on-Ceramic, MoP: Metal-on-Polyethylene, CoP: Ceramic-on- Polyethylene, PHACT: Prosthetic Hip Associated Cobalt Toxicity, ppb: parts per billion.

The second most reported complaints were grouped in the cardiovascular origin. We found 71 suspected cobalt-induced cardiovascular complaints after primary and/or revision hip surgery. The described cardiovascular symptoms divers from dyspnea (N=25; 31.6%), cardiomyopathy (N=12; 15.2%), heart failure (N=10; 12.7%) to cardiogenic shock (N=4; 5.1%) (table 3).

Another systemic problem, often related to cobalt toxicity, is hypothyroidism or thyroid dysfunction. We found 9 patients (11.4%) with proven thyroid abnormalities. A total of 17 (21.5%) patients described fatigue and nine had thyroid dysfunction. Of these 9 patients, only 3 patients had also proven thyroid dysfunction, in all other patients the cause of fatigue had not been investigated or described.

A total of 32 (40.5%) patients were recorded with hip pain as one of the symptoms. Despite this is no systemic complaint, we felt obligated to describe this symptom as it is most likely related to (early) failure of the hip prosthesis.

In all patients who received treatment for the symptoms, by either removing the prosthesis or by medication, the symptoms reduced considerable.

PHACT and blood cobalt concentrations

The mean cobalt concentration in blood at which the systemic symptoms were related was 572.0 ± 962.2 ppb for the total group. However, these concentrations differ greatly between the different bearings. The mean cobalt toxicity level for specific MoM-, revised CoC-, and other bearings were respectively 123.7 ± 96.8 ppb, 1078.2 ± 1267.5 ppb, and 379.4 ± 369.3 ppb. Table 5 described the mean cobalt concentration between the MoM- and revised CoC-bearings and 3 major systemic symptoms; neurological, central/peripheral and sensory, and cardiovascular. There was no noticeable difference between the cobalt toxicity concentrations and the developed symptoms in the two bearings. After revision of the MoM-bearing or a second revision of the earlier fractured CoC-bearing, cobalt concentrations decreased in almost all reported patients.

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Table 3. Demographics of all bearings (n= 79)

	Primary Bearing		
	MoM (n= 38)	CoC (n= 32)	Other (MoP (n= 2), CoP (n= 2), unknown (n= 5)
Variable	Total	Total	Total
Primary surgery			
Mean age at primary surgery in years (SD)	56.2 (14.9)	50.5 (13.1)	54.4 (19.9)
Indication for primary surgery (%)			
• Primary osteoarthritis	16 (42.1)	11 (34.4)	3 (33.3)
• Avascular necrosis	2 (5.3)	4 (12.5)	1 (11.1)
• Fracture	3 (7.9)	1 (3.1)	0 (0)
• Dysplasia	2 (5.3)	0 (0)	0 (0)
• Hip pain	0 (0)	1 (3.1)	0 (0)
• Unknown	15 (39.5)	15 (46.9)	5 (55.6)
Male/Female (%)	20/13 (52.6/34.2)	20/12 (62.5/37.5)	6/2 (66.7/22.2)
Primary PHACT complaints (%)	34 (89.5)	1 (3.1)	3 (33.3)
Revision PHACT complaints (%)	4 (10.5)	31 (96.9)	6 (66.7)
Cobalt toxicity level in ppb	123.7 (96.8)	1,078.2 (1,267.5)	379.4 (369.3)
Mean age at onset of symptoms in years (SD)	58.3 (12.9)	59.3 (10.9)	58.5 (11.5)
Mean time in years at onset of symptoms after primary surgery (range)	2.1(0-13)	8.8 (4-15)	4.1(2-12)
Revision surgery			
Mean age at revision surgery in years (SD)	60.7 (11.2)	56.9 (11.4)	58.5 (8.8)
Indication for revision surgery (%)			
• Systemic symptoms	29 (76.3)	1 (3.1)	2 (22.2)
• Fracture CoC	0 (0)	29(90.6)	2 (22.2)
• (chronic) Pain	3 (7.9)	1 (3.1)	0 (0)
• Recurrent dislocations	2 (5.3)	0 (0)	0 (0)
• Protrusion acetabulum	1 (2.6)	0 (0)	0 (0)
• Fracture	1 (2.6)	0 (0)	0 (0)
• Osteolysis	1 (2.6)	0 (0)	0 (0)
• Unknown	1 (2.6)	1 (3.1)	5 (55.6)
Bearing after revision (%)			
• MoM	0 (0)	6 (18.8)	0 (0)
• CoC	0 (0)	0 (0)	0 (0)
• MoP	5 (13.2)	21 (65.6)	2 (22.2)
• CoP	12 (31.6)	0 (0)	0 (0)
• ToP	1 (2.6)	0 (0)	0 (0)
• CoM / MoC	1 (2.6)	3 (9.4)	0 (0)
• Girdlestone	2 (5.3)	0 (0)	0 (0)
• Not suitable	16 (42.1)	0 (0)	0 (0)
• Unknown	1 (2.6)	2 (6.25)	6 (66.7)
Mean follow up time in months (SD)	13 (12.2)	11 (13.5)	15 (25.3)

SD: standard deviation, MoM: Metal-on-Metal, CoC: Ceramic-on-Ceramic, MoP: Metal-on-Polyethylene, CoP: Ceramic-on- Polyethylene, PHACT: Prosthetic Hip Associated Cobalt Toxicity, ppb: parts per billion, ToP: Titanium-on-Polyethylene, CoM: Ceramic-on-Metal, MoC: Metal-on-Ceramic.

Table 4. All Systemic symptoms (n = 321; 100.0%) reported in 79 patients

NEUROLOGICAL	Total number of patients with specific complain (% of total = 79)
Central and Peripheral (n = 62; 19.3%)	
Cognitive/memory/concentration	16 (20.3)
Paraesthesia/Anesthesia	13 (16.5)
(Poly)Neuropathy	8 (10.1)
Proprioception loss / difficulty walking	7 (8.9)
Headache	4 (5.1)
Hyposthenia / Asthenia	3 (3.8)
Spasm / Muscle cramps	3 (3.8)
Lower motor neuron syndromes	2 (2.5)
Axonopathy	1 (1.3)
Bulbar palsy	1 (1.3)
Convulsions	1 (1.3)
Neuropatic pain	1 (1.3)
Parkinson	1 (1.3)
Tremors	1 (1.3)
Sensory (visual, auditory, gustatory, olfactory, somatosensory, and vestibular, n = 77; 24,0%)	
Hearing impairment / loss	34 (43.0)
Visual impairment / Retinal dysfunction	25 (31.6)
Dysgeusia / Metallic taste	9 (11.4)
Tinnitus	5 (6.3)
Vertigo	2 (2.5)
Loss of smell / Anosmia	1 (1.3)
Optic nerve athrophy	1 (1.3)
CARDIOVASCULAR (n = 71; 22.1%)	**Total number of patients with specific complain (%)**
Dyspnoe/Apnoe/Orthopnea	25 (31.6)
(Peri)cardiomyopathy	12 (15.2)
Heart failure	10 (12.7)
Tachycardia	5 (6.3)
Cardiogenic shock	4 (5.1)
Exertional chest tightness /pain	4 (5.1)
Oedema	4 (5.1)
Pericarditis	2 (2.5)
Hypertension	2 (2.5)
Syncope	2 (2.5)
Pericardial effusion	1 (1.3)

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GASTROENTEROLOGY (n = 12; 3.7%)	**Total number of patients with specific complain (%)**
Diarrhea	3 (3.8)
Nausea	3 (3.8)
Vomiting	3 (3.8)
Anorexia	2 (2.5)
Liver failure	1 (1.3)
MUSCULOSKELETAL (n = 37; 11.5%)	**Total number of patients with specific complain (%)**
Arthromyalgia	1 (1.3)
Decreased muscle mass	1 (1.3)
Polyarthralgia	1 (1.3)
Polymyalgia	1 (1.3)
General stiffness	1 (1.3)
SKIN/HAIR (n = 8; 2.5%)	**Total number of patients with specific complain (%)**
Rash/dermatitis/sarcoid-like	6 (7.6)
Diaphoresis	1 (1.3)
Hair loss	1 (1.3)
THYROID (n = 9; 2.8%)	**Total number of patients with specific complain (%)**
Hypothyroidism/Thyroid dysfunction	9 (11.4)
MENTAL / PSYCHOSOCIAL (n = 25; 7.8%)	**Total number of patients with specific complain (%)**
Fatigue	17 (21.5)
Depression	4 (5.1)
Anxious	2 (2.5)
Insomnia	2 (2.5)
OTHER (n = 20; 6.2%)	**Total number of patients with specific complain (%)**
Weight loss	7 (8.9)
Weakness	4 (5.1)
Fever	2 (2.5)
Malaise	2 (2.5)
Polydipsia	2 (2.5)
Multi-organ failure	1 (1.3)
Polycythemia	1 (1.3)
Uncontrolled diabetes	1 (1.3)

Table 5. The total number of the three most presented systemic symptoms in relation with the cobalt toxicity level in the two most reported bearings (MoM and CoC).

Major Systemic Symptoms	Bearing-type and Cobalt Level (ppb)			
	MoM, n=	Mean Cobalt (SD)	CoC, n=	Mean Cobalt (SD)
Neurological C/P	17	127.2 (110.9)	16	889.1 (574.9)
Neurological Sensory	13	119.4 (98.7)	19	1000.1 (517.9)
Cardiovascular	16	169.0 (100.2)	19	778.4 (504.4)

SD: standard deviation, MoM: Metal-on-Metal, CoC: Ceramic-on-Ceramic, C/P: central and peripheral, ppb: parts per billion.

Discussion

The present review shows that PHACT is mostly seen in primary MoM- and after revision of a (fractured) CoC-bearings for a MoP or MoM articulation. PHACT is a relevant and serious complication with severe systemic symptoms in the neurological, cardiovascular and thyroid system.

It was only after the recall of several MoM prostheses in 2010 that PHACT was increasingly associated to this type of bearing [6, 15]. Before that, only Jones et al. described several cases with cobalt induced systemic issues in the McKee hip (1st generation MoM). In this case series (7 cases), the most frequent mentioned symptom was hip pain and showed increased concentrations of cobalt ions in urine and joint fluid [25]. Three other reports before 2010 by Oldenburg et al., Rizzetti et al. and Steens et al., showed cobalt related problems in revised ceramic bearings [26-28].

In primary MoM-implants the bearing surfaces can release metal particles through corrosion and adhesion (induced by wear). After revision of a (fractured) CoC-bearing to a metal containing articulation (e.g. MoP or MoM), potentially remaining small ceramic particles in the soft tissue and joint space can cause massive abrasion on the metal surface through three-body wear. All mechanisms of particle release may contribute not only to local adverse reactions, but also to potential systemic cobalt toxicity [8, 9].

Limitations
There are some limitations that should be mentioned. Since there are no comparative studies, the present review consists mainly of case reports. Therefore, a publication bias is not ruled out and case reports are considered low quality research. To minimize these limitations, we have assessed the articles on quality by two different methods as guidance for a systematic review methodology publication. As

suggested by the Cochrane Handbook we used the NOS to determine the RoB and assess the quality [22]. Since this questionnaire is not entirely consistent with the assessment of case reports we also used the checklist suggested by Murad et al.[24]. A second major limitation is the lack of controlled comparison studies, no clear reported patient histories and a wide range of blood cobalt ion concentrations. Because of that, a direct relationship between the presented symptoms and elevated cobalt concentrations can not be proven. Some of the reported symptoms can also occur independent from cobalt toxicity and might relate to common health issues or are associated with age. However, we were able to describe and present as adequate as possible the most reported symptoms associated with cobalt toxicity and high probability.

PHACT related to type of bearing

The present review showed PHACT in 38 patients with a MoM-bearing, of which 34 (89.5%) were detected within 2.1 (range 0-13) years after the primary surgery. This is in contrast with the 32 described revised CoC-bearings. In these bearings, only 1 (3.1%) patient had PHACT related complications after primary surgery, whereas 31 (96.9%) patients experienced PHACT within 2.4 (range: 0-9) years after revision surgery. In 29 (93.5%) of these revision cases the indication was a fractured CoC-bearing, plus, all the bearings used in the revision surgery contained at least one metal component (table 3).

PHACT related systemic symptoms

The three most affected systems in patients with cobalt toxicity are in the sensory-, neurological- and cardiovascular systems. The neurotoxic effects of cobalt have already been well established in multiple animal studies [12, 27, 30]. In addition, some case series describe the neurotoxicity in patients after the treatment with cobalt for anemia. Tinnitus and deafness, but also paresthesia and ataxia seem associated with the use of cobalt [12].

All reviewed reports presume a direct relationship with increased blood cobalt concentrations. Within the sensory system, a total of 77 symptoms were described of which the most involved were hearing (N=34; 44.2%) and visual impairment/loss. Most of these symptoms diminished after revision of the prosthesis and a decrease in blood cobalt concentrations was shown. The neurological problems contain mainly cognitive, memory and concentration dysfunction (N=16; 25.8%), as well as paresthesia/anesthesia (N=13; 21.0%). Patients with these symptoms also improved after explanting or revision of the hip prosthesis.

The second most reposted complaints were grouped in the cardiovascular origin (N=71; 22.1%). Of these, dyspnea/apnea/orthopnea (N=25; 31.6%), cardiomyopathy (N=12; 15.2%), heart failure (N=10; 12.7%) and cardiogenic shock (N=4; 5.6%) were most described. The 4 patients with a cardiogenic shock showed cobalt concentrations from 25 ppb to 652 ppb, however a clear dose response effect of the cobalt in these cases could not be established. Of these 4 patients, 1 died due to the cardiogenic shock, 1 needed a heart transplantation and 2 others clinically recovered after explanting the hip prosthesis.

Thyroid dysfunction in relation to cobalt toxicity is also well described in literature, and proven in 9 reported patients (11.4%) [31]. Another symptom, often mentioned in relation with thyroid dysfunction, is fatigue. A total of 17 patients reported fatigue of which only 3 had a proven thyroid dysfunction. In all other cases there was no thyroid dysfunction described. If we combine the two different groups a total of 23 patients (29.11%) may have cobalt related thyroid issues. This will make the thyroid dysfunction a third major affected systemic system, however we could not prove this.

PHACT and blood cobalt concentrations

Most published reports provide a toxicity level of cobalt concentration in their cases, however this concentration divers between all patients and different bearings. The cobalt levels associated with systemic toxicity were considerably higher in patients with revised CoC-bearings when compared to patients with a primary MoM-bearing (mean of 1078.2 ppb and 123.7 ppb respectively - see table 5). Our assumption is that corrosion- and adhesion-related metal exposition in MoM-bearings is more gradually and slower than the massive release of cobalt containing metal wear through three-body related abrasion in fractured CoC-bearings, which have been revised with metal-containing components. Another possible explanation is the awareness of local and systemic problems of the metal ions in MoM-bearings. As a result, clinicians are more likely to link sudden or unexplained systemic issues to the hip prosthesis.

Unfortunately, we found no controlled studies to definitively link the systemic clinical findings with the elevated blood cobalt concentrations and we were unable to determine a safe upper limit threshold for cobalt toxicity.

Conclusion

Since many MoM-bearings are still in situ, we can expect more PHACT cases. Unfortunately, the reported cobalt concentrations differ substantially between the

available case studies. Therefore, it is not possible to provide clear threshold levels for cobalt-related toxicity from this analysis. Nevertheless, clinicians should be aware that patients with a MoM- or revised CoC-bearing are at risk for developing systemic problems. Especially new onset systemic diseases related to neurological, cardiovascular and/or thyroid related symptoms could be due to elevated cobalt concentrations. We also recommend not to use a metal-based articulation in the revision of a fractured ceramic bearing and suggest keeping a close follow-up with yearly blood cobalt concentration controls in patients with MoM-bearings or a revised fractured CoC-bearing.

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7

Chapter VIII

Self-Reported Systemic Complaints in Patients with Metal-on-Metal Hip Arthroplasty

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What makes something special is not just what you have to gain, but what you feel there is to lose

(Andre Agassi)

Abstract

Introduction

An increase in blood serum metal ion levels is seen after implantation of all metal-on-metal (MoM) hip prosthesis. Systemic complaints contributed to raised cobalt ion concentrations in patients with MoM arthroplasty may lead to a variety of symptoms. The aim of this study is to investigate self-reported systemic complaints in association with cobalt ion concentrations in patients with any type of MoM hip prosthesis.

Methods

A cohort study was conducted. Patients with both unilateral and bilateral, resurfacing and large head metal on metal total hip arthroplasties (LHMoM THA) were included. Cobalt ion concentrations were measured by inductively coupled plasma mass spectrometry. Based on the known cobalt toxicity symptoms of case-reports and toxicology reports a new non-validated questionnaire was developed. Analysis was performed on two groups; a low cobalt ion concentration group and a high cobalt ion concentration group.

Results

A total of 62 patients were included with a mean age at surgery of 60.8 ± 9.3 years and a mean follow up of 6.3 ± 1.4 years. Mean cobalt ion concentrations were 104 ± 141 nmol/L (9–833). Based on the different thresholds (120–170 or 220 nmol/L) the low cobalt ion concentration group consisted of 44 (71%), 51 (82%) or 55 (89%) subjects respectively. In the 120 nmol/L and 170 nmol/L thresholds a significant difference in age was found. The composite score for OVS increased from 54% to 57%–68% with rising threshold value, a hint at the correlation between ion concentration and symptom prevalence

Discussion

Ocular-vestibular symptoms were more common in high cobalt ion concentration groups for the three threshold levels tested and with increasing prevalence for higher threshold values. With regards to proactively inquired, self-reported symptoms the threshold where effects may be present could be lower than values currently applied in clinical follow-up

Introduction

An increase in blood serum metal ion levels is seen after implantation of all MoM hip prosthesis due to release from the metal surface directly, more so during articulation and corrosion of the bearing surfaces. Peak concentrations are reached at 9 to 12 months postoperative, hereafter an equilibrium is attained between metal ion release from the implant and metal ion discharge from the body (e.g. via urine)[1]. Design of the prosthesis, component positioning, contact patch to rim (CPR) distance, smaller joint sizes and renal impairment are factors which might influence metal ion concentrations after this period [2, 3]. The continuous exposure to metal ions can result in soft tissue reactions and raised metal ion concentrations in blood, serum and urine [4, 5]. The bearing surfaces in MoM prosthesis consist of cobalt, chromium and molybdenum. One of the most used hip resurfacing systems, Birmingham Hip Resurfacing (BHR), consists of ±60% cobalt, ±30% chromium, ±5% molybdenum and ±1% of nickel, manganese, carbon, silicon and iron [6]. The toxicity of the trivalent (III) form of chromium is low, as opposed to the hexavalent (VI) form [7]. The chromium ions released by MoM prosthesis are of the trivalent (III) form, and therefore non-hazardous [8]. This in contrast to released cobalt ions. Cobalt intoxication or cobaltism is mostly known from industrial exposure, medicinal use and beer additives [9]. This was further substantiated by a systematic review showing a correlation between symptom severity and cobalt ion concentrations but not with chromium ion concentrations [10]. Several case-reports of cobalt toxicity after hip arthroplasty have been published in the last decade, even fatal cases [11, 12]. Systemic complaints in patients with MoM arthroplasty are also known as 'Prosthetic Hip-Associated Cobalt Toxicity' (PHACT) and may lead to a variety of symptoms: neuro-ocular toxicity (tinnitus, vertigo, deafness, blindness, convulsions, headaches and peripheral neuropathy), cardiotoxicity and thyroid toxicity. Nausea, anorexia and unexplained weight loss have been described [13-16]. It was shown that subjects with well functioning MoM hips have more structural and functional differences in organs (heart, liver, and spleen) and a changed structure of the visual pathways and the basal ganglia compared with a conventional total hip control group [17-19]. Thus, systemic effects from metal ions even with well functioning implants or with ion concentrations lower than those associated with known adverse effects may exist and warrant investigation. However, little is known in current literature about the clinical interpretation of raised metal ion concentrations and there potential systemic effects [15]. One can expect a relevant difference between complaints pro-actively self-reported or complaints specifically investigated. In the first case, patients may not report because these events are not so common, not so strong or not associated with the procedure to become reported, although they

may exist and indicate an effect. The aim of this study is to investigate self-reported systemic complaints in association with cobalt ion concentrations in patients with any type of MoM hip prosthesis.

Materials and Methods

A cohort study was conducted between October 2012 and December 2016. The cohort was initially selected for another study; the methods are described in detail elsewere [20]. Patients with both unilateral and bilateral, resurfacing and large head metal on metal total hip arthroplasties (LHMoM THA) were included for the current study. Systemic symptoms were not a presenting complaint in any of these subjects.

Cobalt and chromium ion concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS) using the NexION® 300X ICP-MS (PerkingElmer, Waltham, Massachusetts, United States) at Ziekenhuis Groep Twente, The Netherlands. The first 5mL of each vena punction was disposed, hereafter the blood was collected in a tube (BD Vacutainer® Trace Element, Franklin Lakes, New Jersey, United States) [21]. The blood was shipped within a week from collection and until then stored in a refrigerator at a temperature of 2°-8°C. Concentrations are described in nmol/L. Conversion from nmol/L to ug/L (ppm) is by multiplication with 0.052 for chromium and 0.059 for cobalt.

Based on the known cobalt toxicity symptoms of case-reports and toxicology reports a new non-validated questionnaire was developed. The subjects were asked to answer 17 questions on general health since placing of the MoM hip prosthesis. The questions were subdivided in general questions/symptoms, ocular-vestibular symptoms (OVS), neurological symptoms, emotional health and cardio- and thyroid toxicity symptoms. The answer options were yes and sometimes (score 1) and no (score 0). Combined scores were optained per group and a combined neuro-ocular-vestibular composite score (NOVCS). The Hip disability and Osteoarthritis Outcome Score Physical function Shortform (HOOS-PS) was obtained and scored from no difficulty (0) to extreme difficulty (100) [22].

This study was performed in compliance with the 1975 Declaration of Helsinki, as revised in 2000, was studied and approved by the IRB (METC Zuyd, Heerlen, The Netherlands, IRB Nr. 10N72) and conducted in accordance with the guidelines for Good Clinical Practice (GCP).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (International Business Machines Corporation, Armonk, New York, United States). Independent samples T test and Fisher's Exact Test were used. Analysis was performed on two groups; a low cobalt ion concentration group and a high cobalt ion concentration group. The upper limit of well functioning prosthesis was set at 170 nmol/L (10 µg/L), as stated by the Dutch orthopaedic society (Nederlandse Orthopaedische Vereniging (NOV)) and described by Verhaar [23]. We also performed analysis with two arbitrarily chosen thresholds, a lower limit of 120 nmol/L and a higher one of 220 nmol/L to investigate whether for systemic effects another concentration level may be better suited than one which is established for known adverse effects. Results are shown as means ± standard deviation and [range] or (percentage) with p<0.05 as significance level.

Results

A total of 62 patients (58% men) with 71 prosthesis were included with a mean age at surgery of 60.8 ± 9.3 years (41.6 – 78.1) and a mean follow up of 6.3 ± 1.4 years (3.7 – 9.6). There were 44 resurfacing and 27 LHMoM THA. The mean interval between the metal ion concentration measurement and fulfilling of the questionnaires was 1.4 ± 0.8 years (0.2 – 2.5). Mean cobalt and chromium ion concentrations were 104 ± 141 nmol/L (9 – 833) and 95 ± 130 nmol/L (6 – 592), respectively (Table 1).

Table 1. Baseline Characteristics

Gender	M 36 (58%) / F26 (42%)
Age at OR (years)	60.8 ± 9.3 [41.6 – 78.1]
Follow-up (years)	6.3 ± 1.4 [3.7 – 9.6]
Resurfacing (number of)	44
LHMoM (number of)	27
Unilateral (number of)	53
Bilateral (number of)	9
Interval (years)*	1.4 ± 0.8 [0.2 – 2.5]
Cobalt (nmol/L)	104 ± 141 [9 – 833]
Chromium (nmol/L)	95 ± 130 [6 – 592]
HOOS-PS(0-100)	18.9 ± 17.9 (0 – 67.9)

* Interval between measuring of metal ion concentrations and completing questionnaires

Based on the different thresholds (120 – 170 or 220 nmol/L) the low cobalt ion concentration group consisted of 44 (71%), 51 (82%) or 55 (89%) subjects respectively. In the 120 nmol/L and 170 nmol/L thresholds a significant difference in age was found. The composite score for OVS increased from 54% to 57% to 68% with rising threshold value, a hint at the correlation between ion concentration and symptom prevalence. Also, the NOVCS of the high cobalt ion concentration group in the 220 nmol/L threshold was significantly higher (p = .047). A composite score for cardio- and thyroid toxicity showed no significant differences between the groups (Table 2).

Discussion

This study aimed to investigate if cobalt ion concentrations commonly observed with MoM hip arthroplasty may result in more frequent self-reported systemic complaints above various cobalt ion level thresholds. The main finding of this study was that OVS are more common in patients with high cobalt ion concentrations, independently of the thresholds investigated (120 – 170 or 220 nmol/l). In accordance, the composite score of OVS was significantly higher in the high concentration group for all three threshold values tested and the score increased with raising the threshold value.

Subjects in the current study reported tinnitus (31% overall) and hearing loss (40% overall). This is in agreement with Leikin et al. who reported tinnitus and/ or hearing loss in 7 of their 26 (27%) subjects with MoM arthroplasty with a mean age of 55.6 years and median cobalt ion concentration of 14.1 µg/L (239 nmol/L). Patients were referred by self-referral, primary care physicians, orthopaedic physicians, poison centers and hip-arthroplasty manufacturers. Identification of symtoms was performed by the use of a clinic standard medical toxicology health history form [15]. Also Prentice et al. reported similar self-reported tinnitus (21-33%) and hearing problems (33%) in patients with MoM arthroplasty [24]. The average number of patients in the general population with tinnitus is far lower (14%) [15]. Rizzeti et al. and Bradberry et al. described tinnitus and hearing loss as symptoms of cobalt toxicity [12, 13]. This is further substantiated by the fact that the current study reports more subjects with tinnitus in the high cobalt ion concentration group at higher thresholds and with increasing threshold values. In contrast to these results, van Lingen et al. did not find a correlation between self-reported neurotoxic complaints and cobalt ion concentrations [25]. Only 10% of subjects were found to have cobalt ion concentrations >170 nmol/L, compared with 18%

in the current study. This might have resulted in an underpowered study to detect neurotoxic effects. Also, van Lingen et al. used the NCS-60 questionnaire which is not designed and not validated for cobalt toxicity. The NCS-60 is a validated Dutch questionnaire mainly used to determine exposure to neurotoxic compounds in workers and in the evaluation of suspected neurotoxicity [26]. The current study used a questionnaire which has not been validated but was designed to specifically detect symptoms of cobalt toxicity, as opposed to the generic NCS-60. Prentice et al. could not associate slightly elevated cobalt ion concentrations (<10nmol/L), with clinically demonstrable visual or auditory dysfunction [24]. The cobalt ion concentrationsin the cohort of Prentice et al. might be too low to generate visual or auditory dysfunction.

The clinically best-to-use cobalt ion concentration threshold is debatable, for well functioning hips, for the likely existence of pseudotumors and for possible cobalt toxicity. Tower advised neurological and cardiac assessment for patients with a cobalt concentration ≥ 7 μg/L (119 nmol/L) [27]. In the 18 cobalt toxicity case reports reported by Bradberry et al. subjects showed a mean cobalt ion concentration of 398 μg/L (6754 nmol/L)[13.6 – 6521μg/L][13]. Those patients with a failed ceramic prosthesis, revised with a metal-containing prosthesis, showed blood cobalt concentrations of 506 μg/L (8587 nmol/L) [353 – 6521 μg/L]. Patients with a primary MoM prosthesis, like all subjects in the current study, showed a blood cobalt concentration of 34.5 μg/L (586 nmol/L) [13.6 – 398.6μg/L]. In constrast, a review of Paustenbach et al. concluded that significant systemic complaints of cobaltism will not occur when concentrations of cobalt ions stay below 300 μg/L (5091 nmol/L)[28]. Leikin et al. and Ho et al. could not correlate cobalt and chromium ion concentrations with the incidence of systemic symptoms [15, 16]. The study by Ho et al. is a follow-up study of the aforementioned Leikin et al., a part retrospective and part prospective review of patients referred to toxicology clinics in London, UK and in the USA recorded in the Toxicology Investigators Consortium (ToxIC) Registry from June 2011 to June 2015.

Also the current study has some limitations. The study is uncontrolled to the extent, that there is no matched group with a non-MoM bearing or a matched group without a THA to serve as a comparator in a general or similar population. However, comparison is made between the high and low ion concentration groups for three threshold values. Patients were informed on the cobalt ion concentrations which could potentially affect the reported symptoms. A patient reported outcome measure (PROM) asking for complaints may bias patients towards reporting something for which they only generate awareness via the questionnaire but this new approach

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Table 2. Occurence of self-reported symptoms divided by different threshold

	Occurence at threshold 120 nmol/L			Occurence at threshold 170 nmol/L			Occurence at threshold 220 nmol/L		
	<120	>120	p	<170	>170	p	<220	>220	p
Baseline									
Number of subjects	44 (71%)	18 (19%)		51 (82%)	11 (18%)		55 (89%)	7 (11%)	
Age at OR (years)	57.4 ± 7.4 [41.6 – 73.8]	68.4 ± 7.7 [55.2 – 78.1]	<.001	59.4 ± 8.7 [41.6 – 78.1]	65.9 ± 8.7 [55.2 – 77.7]	.029	60.2 ± 9.1 [41.6 – 78.1]	63.4 ± 8.5 [55.2 – 77.0]	.382
Follow-up (years)	6.7 ± 1.5 [3.7 – 9.6]	5.6 ± 1.1 [4.0 – 8.2]	.004	6.5 ± 1.5 [3.7 – 9.6]	5.9 ± 1.1 [4.8 – 8.2]	.239	6.4 ± 1.5 [3.7 – 9.6]	6.2 ± 1.3 [4.9 – 8.2]	.824
Cobalt (nmol/L)	38 ± 24 [9 – 100]	258 ± 178 [122 – 833]	<.001	52 ± 41 [9 – 158]	334 ± 193 [170 – 833]	.001	62 ± 54 [9 – 207]	418 ± 199 [266 – 833]	.003
HOOS-PS (0-100)	18.9 ± 19.4 [0 – 67.9]	17.9 ± 14.3 [0 – 46.1]	.846	19.2 ± 18.5 [0 – 67.9]	16.3 ± 15.1 [0 – 46]	.628	18.2 ± 18.2 [0 – 67.9]	21.8 ± 16.3 [4.6 – 46.1]	.621
General									
Known thyroid disease	11%	6%	.662	10%	9%	1.000	11%	0%	1.000
Known CNS disease[1]	9%	11%	1.000	10%	9%	1.000	9%	14%	.528
Headache	36%	28%	.569	35%	27%	.735	35%	29%	1.000
Ocular-Vestibular symptoms									
Vision / Eyes	52%	61%	.058	51%	73%	.317	53%	71%	.442
Hearing	34%	56%	.016*	39%	45%	.744	38%	57%	.425
Tinnitus	28%	39%	.545	28%	45%	.294	28%	57%	.189
Dizziness	36%	61%	.095	39%	64%	.186	40%	71%	.223
Composite	38%	54%	.023*	39%	57%	.043*	40%	68%	.008*
Neurological symptoms									
Tremor	14%	29%	.263	16%	27%	.400	17%	29%	.599
Paresthesias phalanges	30%	18%	.518	29%	18%	.710	28%	14%	.663
Deafness phalanges	16%	24%	.481	16%	27%	.400	17%	29%	.599
Composite	20%	24%	.685	20%	24%	.638	20%	24%	.776

Emotional Health									
Fear	16%	11%	1.000	16%	9%	1.000	15%	14%	1.000
Irritation	32%	44%	.390	37%	27%	.732	35%	43%	.690
Depression	11%	11%	1.000	10%	18%	.597	11%	14%	1.000
Composite	20%	22%	.693	21%	18%	.816	20%	24%	.774
Combined Neuro-Ocular-Vestibular Composite Score	28%	29%	.707	29%	38%	.228	29%	40%	.047*
Cardio- and Thyroid symptoms									
Weight loss	12%	28%	.143	14%	27%	.367	17%	14%	1.000
Tiredness	68%	61%	.768	67%	64%	1.000	64%	86%	.406
Weakening	41%	33%	.775	37%	45%	.736	36%	57%	.186
Palpitations	20%	22%	1.000	24%	9%	.431	22%	14%	1.000
Composite Score	47%	36%	.140	35%	36%	1.000	35%	43%	.408

* Significant at $p < 0.05$

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also differentiates this study from previous reports relying on generic PROM's or proactively reported complaints. The aim was to correlate symptoms with cobalt ion concentrations, presumably due to a MoM prosthesis, but it might be possible that other factors influenced cobalt ion concentrations or self-reported symptoms. Patient related factors such as allergies, diabetes, diet, medication and occupation, were not (fully) taken into account.Toxicity of cobalt is related to the unbound (free) form of cobalt (Co^{2+}), whereas most cobalt is bound to albumin. The refined biokinetic model of Unice et al. states that the concentration of unbound cobalt in the circulation raises and toxicity occurs at lower concentrations in susceptible subjects and in certain conditions such as kidney failure, iron deficiencies, sepsis, malnutrition and use of medication [29]. The used questionnaire was not formally validated but it was purely designed for the detection of symptoms of cobalt toxicity. It was not the intention of this study to create a new and validated questionnaire, but to study a possible effect yet unnoticed due to the lack of validated tools which are targeted and not generic. The interval between obtaining the questionnaire and the metal ion concentrations was rather large with 1.4 ± 0.8 years (0.2 – 2.5). We aimed at measuring the steady-state concentrations so that the time difference between ion level assessment and PROM shall be less critical, than during the transient phase.The current study also did not measure renal functions, but severe renal insuffiencies can be ruled out and only milder forms which have produced no symptoms or have not yet been diagnosed may exist. Cobalt and chromium ions are rapidly excreted by the kidneys: 80-90% of cobalt ions within days and 60% of chromium ions within 8 hours [3, 5].

Although mild variations in metal ion concentrations might exist, the current study was designed to measure metal ion concentrations at a steady-state after the running-in period of 9-18 months [1]. Also, Lainala et al. showed no association between metal ion concentrations and mild or moderate renal insufficiency [30].

A significant difference in age between the groups was found for the 120 nmol/L and 170 nmol/L thresholds. This might have influenced the reported symptoms. Normal aging, with reduction in vision and hearing for example, might be confused with symptoms caused by increased cobalt ion concentrations and thus may have influenced the reported symptoms. The prevalence of hearing impairment for males in Dutch general practice is 3.9% in agegroup 55-59 years, 6.3% in agegroup 60-64 years, 9.7% for agegroup 65-69 years and 13.4% for agegroup 70-74. For females this is 3.6%, 5.1%, 6.9% and 9.0% respectively [31]. Hearing impairment is thus more frequent with increasing age, but does not fully explain the differences found in OVS in the current study, although these specific confounding factors (e.g. age) was not controlled for.

Further research should focus on a larger cohort of MoM arthroplasties and investigate prevalence but also include symptom severity and frequency. The questionnaire used should be optimalized and focus on the main outcome of the current study. To optimize associations a shorter period of time between metal ion assessment and PROMs should be guaranteed. A long term follow-up like in this study must be considered as some systemic effect, e.g. depression, may need more time to manifest themselves.

This study aimed to detect a trend in self-reported systemic complaints in patients with metal-on-metal hip arthroplasty due to raised cobalt ion concentrations. Ocular-vestibular symptoms were more common in high cobalt ion concentration groups for the three threshold levels tested and with increasing prevalence for higher threshold values. With regards to proactively inquired, self-reported symptoms the threshold where effects may be present could be lower than values currently applied in clinical follow-up. It is unknown how exposure to elevated metal ion concentrations for a longer period of time affects the health of aging subjects. Further research with a larger cohort and more standardized questionnaire is necessary to uncover previously undiscovered or under-reported effects warranting investigation.

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8

Chapter IX

General Discussion

It is not the size of a man but the size of his heart that matters

(Evander Holyfield)

Total hip arthroplasty (THA) is a successful procedure for patients suffering from pain, joint stiffness, functional disability and limitations in their activities, which are most often due to osteoarthritis of the hip. Each year, a million THA procedures are performed worldwide. THA is increasingly offered to younger osteoarthritis patients, and at any age patients tend to have high expectations of their operation and high demands regarding functional outcomes, which increases the need for durability of the different prostheses [1]. Survival in younger patients (<55 years) is inferior to survival among older patients. Due to longer life expectancy, these younger patients will outlive their prosthesis [2].

The design of the prostheses has changed continuously, and materials have been developed to withstand the exposed stresses and to reduce the wear of bearing surfaces. The drive to improve the performance of THA resulted in the re-introduction of metal-on-metal (MoM) implants in the late 1990s and early 2000s [3]. It was shown that in-vivo wear rates of these 'second generation' MoM bearings were almost 100 times lower than those of metal-on-polyethylene (MoP) bearings and that the small particles were less likely to induce the macrophage-induced response observed in MoP bearings, which led to osteolysis ('polyethylene disease') [4, 5]. In particular, hip resurfacing arthroplasty (HRA) was designed for highly active, young patients because of the various theoretical advantages over conventional stemmed MoP THA: low volumetric wear, femoral heads with a large physiological diameter offering stability, near-natural joint kinematics, an increased range of motion compared to THA with a small femoral head diameter, and preservation of the femoral bone, which would enable an easy revision if needed [6].

Since 2004, multiple cohort studies and national registry data of MoM hip implants have shown high failure rates, and the 10-year survival rate threshold of 95% set by the National Institute for Health and Care Excellence (NICE) was not achieved [7, 8]. Many prostheses systems were recalled by their manufacturers. Currently, only a few MoM prostheses are still available [9]. In 2012, the NetherlandsOrthopaedicAssociation (NOV) advised against the use of MoM [10, 11]. However, a large number of patients had already been treated with a MoM prostheses; estimates vary between 1 and 1.5 million patients worldwide [12, 13]. In a report of the Network of Orthopaedic Registries of Europe (NORE) based on data of 11 national registries, the ten-year pooled revision rates were reported to be 12.1% for the HRAs and 15.5% for the stemmed large-head MoM (LHMoM) THA implants [9].

Influence of physical activity

In MoM hip arthroplasty, the metal surfaces are exposed to wear, which results in the release of metal ions. The concentration of metal ions in blood or serum is considered an indirect measure of such volumetric wear. Implant wear is a function of use and thus of a patient's physical activity (PA). This association between PA and implant wear was proven for THA with a polyethylene bearing, and in theory, it also applies to MoM hip arthroplasty [14]. To confirm or disprove this theory, we investigated the relation between objectively measured PA and blood metal ion concentrations in patients with a MoM hip arthroplasty (aim 1). For four consecutive days, PA in daily living was measured during waking hours using an acceleration-based activity monitor (AM). The analysis included data of 62 patients with any type of MoM hip implant (HRA and LHMoM THA), both uni- and bilateral, with a mean age at surgery of 61 years and a follow-up of 6 years. No correlations were found between serum cobalt ion concentrations and PA monitor parameters. The daily step count found in this study was comparable to that of healthy people of the same age, showing that this population with a MoM prosthesis was normally active [15]. At this point, the theory that implant wear is a function of use and thus of patient activity levels could not be confirmed for MoM hip arthroplasty. Since the heterogeneity in this study was a major concern, an attempt was made to solve this issue in the next study, which included a more homogenousgroup (16 subjects with unilateral HRA) with a long follow-up (10-years). During a short time span, metal ion concentrations were measured and PA was monitored, which revealed a statistically significant and clinically meaningful correlation between cobalt ionconcentrations and two distinct parameters of habitual PA: the number of sit-stand-transfers, and high-intensity peaks. No statistically significant association with cobalt ion concentrations was found for the habitual level of time spent walking, the total number of steps, or the percentage of time spent on PA. The cause of increased metal ion concentrations after HRA seems multifactorial, and specific aspects of PA might constitute contributing factors. The qualitative aspects of PA seem more important than the conventionally measured quantitative parameters of PA. While the homogeneity of the study population was an advantage, the study had several limitations: the group size was rather small, metal ion concentrations were not normally distributed, and one subject showed abnormally high cobalt ion concentrations. When this specific subject was excluded from analysis, the correlations between PA and cobalt ion concentrations disappeared. However, also walking cadence, a proxy of walking speed was found to have a trend towards a significant correlation with cobalt ion concentrations. Further research should focus on patients with high metal ion concentrations and the correlation with PA, high-intensity peaks in particular.

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The results of these studies suggest that patients with a MoM hip arthroplasty can walk as much as they desire without the risk of higher cobalt ion concentrations. However, if these patients walk too fast or too intensely (high impacts; qualitative aspects of PA) or execute a higher number of sit-standtransfers (behavior), they are more at risk for higher metal ion concentrations. It seems that general habitual PA such as normal walking does only slightly influence metal ionconcentrations. Only qualitative aspects of PA matter. For patients, it seems safe to engage in activities with low-intensity peaks, such as walking or cycling, without triggering critical wear, which means that they are able to maintain important general health benefits and quality of life. However, with the use of an HRA, it can be suggested by manufacturers and orthopaedic surgeons that patients can perform any type of movement ('sports-hip'), including large impact activities, although these activities have been shown to be especially precarious.

While in the present rehabilitation after THA the focus lies on the quantitative aspects of PA (walking), more attention should be paid to the training of qualitative aspects of PA. A more controlled movement (propriocepsis) could result in fewer high intensity events such as stumbles or falls and in a more controlled sit-stand transfer. This rehabilitation should preferably start prior to the hip replacement, because by improving preoperative functioning, one improves postoperative functioning ('better-in, better-out'), at least in theory. However, literature on this topic is unclear [16, 17]. Further research on MoM hip arthroplasty should focus on a larger cohort of patients, especially those with high metal ion concentrations. The correlation with PA, in particular with its qualitative aspects, should be studied in-depth as an important contributor to the multifactorial aspect of chronically raised metal ion concentrations and their potential risk.

Theoretical advantages

Based on the theoretical advantages, such as the theoretically better implant design features of HRA that are claimed to support a more active lifestyle, the selection of patients for this particular implant (young and active), and the related patient expectations (high preoperative demands on postoperative activity), it can be expected that patients who received HRA would be more physically active after surgery than patients who received a conventional stemmed THA (aim 2). This was the reason for studying objectively measured PA in both groups of patients. The HRA group described earlier was compared with a non-MoM stemmed THA group matched for sex, age at surgery, follow-up since surgery, and BMI. There were no statistically significant differences between group characteristics at baseline. Contrary to expectations, it was

shown that patients with an HRA were not physically more active; the groups showed similar PA monitor parameters.

It is common knowledge that PA provides health benefits, but not every individual participates in sports or is highly physically active. Anxiety and a lack of confidence were found to be the main barriers to participation of adults [18]. PA is influenced by social networks (e.g. the presence or absence of parental control, modelling), the physical environment (e.g. availability and accessibility, prices), the macro environment (e.g. media and advertising) and especially by individual factors (e.g. perceived enjoyment, self-discipline) [19]. The behavior of people, and thus also of patients, depends more on intrinsic factors than on extrinsic ones. While often pain is a reason for decreased PA, it seems that a pain-free hip and improved functional capacity is not necessarily associated with higher PA levels. Patients have their own level and style of PA, which is hardly adaptable.

The importance of PA and its influence on life should be trained and discussed at primary and high school. Sports should be available to everyone, and extra attention should be focused on negative experiences during PA classes at school, because these negative experiences are strong factors in discouraging participation, especially in young women [18]. By doing that, children and adolescents are made aware of the importance of PA and of the dangers of physical inactivity, which is considered a major risk factor for a number of adverse health outcomes. Reaching a daily step count of more than 8,000 steps has been associated with a lower risk of all-cause mortality [20]. However, only 6 out of 32 patients reached this threshold at 10 years after hip arthroplasty. In addition, almost half (13/32) would be considered to be leading sedentary lives with the associated risks of developing non-communicable diseases [15]. No differences were found between subjects with an HRA and those with a conventional stemmed THA with a MoP or CoP bearing. Both implant types enable the same level of PA, and activity levels depend more on individual lifestyle than on implant type. While short-term effects may exist, ageing and related behavioral adaptations or other effects seem to render the theoretical activity benefits of HRA irrelevant at longer follow-up. In addition, the development of ultra-high molecular weight polyethylene (UHMWPE) in to cross-linked UHMWPE (XLPE) led to a decrease in revision rates for THA at long-term follow-up (16 years) from 11.7% for UHMWPE to 6.2% for XLPE. In recent years, antioxidants such as Vitamin E were added to XLPE and showed promising early clinical results [21]. Based on the evolving development and current clinical performances of polyethylene, which does not have the risks known to MoM bearings, it is the golden standard in bearing choice for THA. There seems no role for MoM bearings in current orthopaedic practice.

The theoretical advantages of HRA over stemmed THA should be explored in detail. The introduction of HRA shows how expectations may turn out to differ from reality and outcomes may develop differently than expected. The lack of adequate regulation lies at the base of this problem. While for pharmaceuticals, a phased evidence-based introduction is obligatory, this is not required per definition for orthopaedic implants due to the 510(k) pathways in the United States, for example. Unsafe orthopaedic implants can reach the market. In recent years, more attention has been gained for a phased evidence-based introduction of orthopaedic implants with a pre-market setting to detect early failure modes. One might think of biomechanical studies, radiostereophotometric analysis, implant retrieval and outcome assessment [22]. One of the early failure modes of HRA, which could have been detected in a pre-market setting, was the increased risk of a femoral neck fracture (within 3 months), with a reported prevalence of 1 to 2.5% [23]. Overweight, older female patients were at high risk, presumably due to osteoporosis of the femoral neck. Retrieved femoral heads showed avascular necrosis, while this had not been the indication for surgery [24]. Late failure modes, however, will also occur in the post-market phase. New implant designs, such as MoM, can introduce unexpected types of failure, e.g. pseudotumor formation and cobalt toxicity. Surgeons and national joint registries should be highly alert to these unexpected failures [25].

Worldwide, the expected theoretical advantages of HRA were only partially met, for example by some full distance triathletes, professional tennis player Andy Murray and National Hockey League player Ed Jovanovski [26]. These successful outcomes were especially used by the industries to show the possibilities of HRA and to convince future patients to choose HRA. On the other hand, it is unknown if athletes who were operated with conventional stemmed THA could return to their preoperative high level of sports activity after surgery. No high-quality comparative studies are available. However, most patients are less content due to complications such as femoral neck fractures, highly increased metal ion concentrations, adverse reactions to metal debris and a high change of revision within 10 years (12.1%) [9].

Concerning the high number of problems, it is incredible that, while the NetherlandsOrthopaedicAssociation (NOV) advised against the use of MoM in 2012, it is still possible for patients in the Netherlands to cross national borders and receive MoM HRA abroad. Health insurers play a critical role; they control the funds and health care, while the scientific association (NOV) sets limits to their members concerning MoM hip replacements. In addition, direct to consumer advertising was a new way of promoting HRA, aiming to persuade the patient to choose this

type of treatment. With the World Wide Web being the ideal medium to distribute information, large numbers of people can be reached. However, the quality of distributed information is variable [27]. HRA was advertised as the sporting hip, but in view of the results of this thesis and of the issues mentioned before, it would be more apt to speak of a political or financial hip. Choosing a technique for hip arthroplasty requires detailed information from surgeon to patient and clear insight into trade-offs between benefits and harms – in other words, it requires shared decision making. For orthopaedic surgeons, communication skills are at least as important as surgical skills. As my supervisor said: "a spoken word can be sharper than a knife" (Heyligers). The training of orthopaedic surgeons does not only involve learning to operate, but also setting indications for surgery and learning to be critical of new and existing procedures.

Current developments in prosthesis design are focussing on HRA with a cobalt-chromium femoral component and a cementless acetabular cup with a XLPE-acetabular liner, and on HRA with a ceramic-on-ceramic (CoC) bearing [28, 29]. It would be highly interesting to obtain objectively measured PA both pre- and postoperatively in patients with these types of HRA, and to compare these PA data to those of patients with conventional stemmed THA. It is, however, unsure if these new developments improve current results and solve current problems, or have benefits for multiple parties except for the patient itself. The development of new materials and techniques has to be a proven stepwise and well described process [25].

Outcome assessment
In orthopaedics, patient-reported outcome measures (PROMs) are designed to quantify changes in aspects that are important to patients, such as pain and physical function (PF) [30, 31]. While PROMs are commonly used, they can suffer from their subjective nature, recall bias, ceiling effects, low response and completion rates or transcription errors and the fact that PROMs are a time consuming method [32-35]. In addition, it is unknown if and how PROMs after THA reflect real levels or qualitative aspects of PA in daily life as captured with wearable AMs. Hence, we investigated to what extent objectively measured physical activity is associated with patient-reported physical activity (aim 3). PROMs of various dimensions, general health, disease specific outcome and in particular PF, joint awareness and self-perceived activity levels are correlated with objectively measured PA parameters derived from wearable AMs in subjects with a hip arthroplasty (n=32). The Hip disability and Osteoarthritis Outcome Score Physical Function Short form (HOOS-PS) and physical function subscale of the Short Form (36) (SF-36) were statistically significantly correlated with the daily time walking, the daily total time active and

the number of daily steps. The Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) only showed a statistically significant negative correlated with the age at surgery, but not with any of the objectively measured PA parameters. The correlations found were of moderate strength [36]. In order to reach sufficient content validity, van Poppel et al. recommended that at least duration and frequency should be determined by means of a questionnaire that assesses total PA and should also cover PA in all settings during daily life [37]. Surprisingly, the only questionnaire that meets these recommendations (SQUASH) was found not be correlated with objectively measured PA parameters.

The outcome of THA is influenced by an individual's interpretation and perception of joint functioning. PROMs remain inherently subjective; patients can have difficulties ignoring other negative conditions or illnesses that might have impaired their mobility, general fitness or quality of life [38]. The fact that subjectively reported PA levels and objectively measured PA levels do not correlate may indicate that it is inherently difficult to recall PA durations and frequencies in detail without bias, which challenges the use of PROMs for individual or group outcome studies and suggests that it might be limited to large population-based research, in which sensor-based assessment is not yet possible. For many PROMs, the main determinant of outcome seems to be pain, because patients have difficulties differentiating between pain and functional disability [39, 40]. In addition, PROM data are highly influenced by a patient's postoperative pain relief, which may lead to an overestimation of the actual short-term and long-term changes in physical function [41-44].

A combination of PROMs and AM displays a patient's perception of physical functioning and the practitioner's or researcher's view of objectively determined PA of THA patients. For clinical practice, considering the value of PA for maintaining general health and the importance of restoring PA via surgery such as THA, sensor-based AMs seem to have a very high value in assessing the efficacy of treatments in this health-related dimension or as a tool for improving patient education, awareness and communication. Wearable PA monitoring gives useful information for the assessment of outcome of our treatments, such as THA, in particular in combination with PROMs. PA monitoring seems to deserve a place beside PROMs in the pre- and postoperative phase and follow-up of THA. PA monitoring provides reliable information to the patient and enables the surgeon to warn the patient if deviations from what was expected occur.

Future studies should focus on the changes in health status as measured by PROMs and their correlation with objectively measured PA, for example before

and after total joint arthroplasty. For example, future PA research might focus on the differences in PA after THA with different surgical approaches (e.g., straight lateral, posterolateral, or direct anterior), different bearings and different prosthesis designs.

In current orthopaedic literature, the use of implant registers is increasing [45]. National joint replacement registries are multi-centre databases comprised of thousands of subjects and implants, which allow for objective outcome assessment and possibly for identifying variables of implant failure. Failed arthroplasties are often revised. One of the advantages of HRA was preservation of the femoral bone, which would result in an easy revision if needed. In general, revision procedures are technically challenging and expensive, and although these procedures provide clinical benefit and patient satisfaction, they tend to have a worse outcome than primary THA procedures [46, 47]. The present research used the Dutch Arthroplasty Register (LROI) to determine the outcomes of revision surgery in failed MoM hip arthroplasties and to compare these outcomes to the outcomes of revision of non-MoM hip arthroplasties (aim 4). A total of 3,478 revised implant records were found, 873 of which (25.1%) were MoM implants. Over the course of follow-up, the re-revision risk was 11.5% for MoM implants after slightly more than 5 years and 14.1% for non-MoM THA. The regression model showed that for MoM implants, significant risk factors for re-revision were a periprosthetic fracture as reason for index revision, a MoM articulation after the index revision, and femoral-only revisions. Large numbers of implant records can result in small p-values and narrow confidence intervals, but the statistically significant findings may not always be of clinical relevance, e.g., because functional outcomes are unknown. Joint registries are essential for detecting implant failures and for the phased evidence-based introduction of orthopaedic implants mentioned earlier. However, national arthroplasty registry studies are limited by the compliance of health institutions, completeness and revision surgery as the only outcome criterion [48].

Cobalt toxicity

An increase of metal ion levels in blood serum is seen after implantation of all types of MoM hip prostheses due to release of ions from the metal surface directly and more so during articulation and corrosion of the bearing surfaces [49]. This continuous exposure to metal ions can result in soft tissue reactions and raised metal ion concentrations in blood, serum and urine [50]. Initially, there were concerns that increased cobalt and chromium ion concentrations increased the risk for cancer, but this was proven otherwise in large comparative studies [51, 52]. However, little was known about the clinical interpretation of raised metal ion concentrations and their

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potential systemic effects [53]. An increasing number of case reports describing systemic reactions in relation to elevated serum cobalt, known as Prosthetic Hip-Associated Cobalt Toxicity (PHACT), are available in literature [50, 54]. The systemic complaints in patients with PHACT may lead to a variety of symptoms: neuro-ocular toxicity, cardiotoxicity and thyroid toxicity [55].

The present thesis includes two studies that aimed to determine whether chronically raised metal ion concentrations are associated with systemic complaints (aim 5). First, a systematic review of cobalt toxicity casereports was performed to determine the systematic symptoms described most often and to determine the toxicity threshold level of serum cobalt ion concentration. A total of 79 reported patients were found, with a mean age of 59.0 ± 11.5 years. A primary MoM bearing was used in 38 cases (48%) and in 31 cases (39%), a metal component was used in the revision of a fractured ceramic component. Most of the symptoms involved the sensory system (24%), the most frequently described complaints being hearing and visual impairment or loss. Other frequently reported symptoms were neurological problems (19%), such as cognitive, memory and concentration deficits and paraesthesia or anaesthesia, and cardiovascular complaints (22%), such as dyspnoea, heart failure and cardiomyopathy. The cobalt threshold concentration differed greatly between all reports, which precluded the identification of a clear toxicity threshold.

For a subsequent study, we composed a new non-validated questionnaire based on the known cobalt toxicity symptoms of case-reports and toxicology reports. The questionnaire was answered by 62 MoM hip arthroplasty patients with a mean age at surgery of 61 years and a mean follow-up of 6 years. The composite score for ocular-vestibular symptoms increased from 54% to 57%–68% with rising threshold value (120–170 or 220 nmol/L), which suggests a correlation between ion concentration and symptomprevalence. Subjects in the current study reported tinnitus and hearing loss far more often than patients in the general population [53, 56, 57]. Also, more subjects were found with tinnitus in the high cobalt ionconcentration group at higher thresholds and with increasing threshold values. A PROM asking for complaints may bias patients towards reporting something for which they only generate awareness via the questionnaire, but this new approach also differentiates this study from previous reports relying on generic PROMs or proactively reported complaints. Patients with a MoM hip arthroplasty, independent of the type, should be monitored systemically for the outcome of hip arthroplasty but also concerning systemic complaints, especially for ocular-vestibular symptoms in patients with chronically raised cobalt ion concentrations. It is unknown how exposure to

elevated metal ion concentrations for a longer period of time affects the health of aging subjects. Further research with a large cohort and more standardized questionnaires is necessary to uncover previously undiscovered or under-reported effects warranting investigation.

Conclusion

This thesis showed the potential of monitoring physical activity with the use of wearable activity monitors during the pre- and postoperative follow-up of hip arthroplasty. The influence of physical activity on blood metal ion concentrations in patients with a metal-on-metal hip arthroplasty was demonstrated. It showed that physical activity is an important contributor, which was previously unknown. A statistically significant and clinically meaningful correlation was found between cobalt ion concentrations and distinct parameters of habitual physical activity. Chronically raised cobalt ion concentrations are a potential thread to general health in patients with a metal-on-metal hip arthroplasty. Ocular-vestibular symptoms were more common in high cobalt ion concentrations and with increasing prevalence for higher threshold values. Patients might experience symptoms with thresholds lower than values currently applied in clinical follow-up, only mentioned by patients because these were proactively inquired. In addition, if low-intensity physical activity does not result in excessive wear of the MoM bearing and thus in high metal ion concentrations as the indirect measure of this wear, systemic complaints as a result of chronically raised cobalt ion concentration might be prevented by informing patients about the type of PA that is most beneficial for their wellbeing. In comparison with patients with a conventional stemmed total hip arthroplasty, patients with a unilateral hip resurfacing were not physically more active at 10-year follow-up. Contrary to the expectations that were based on the theoretical advantages of hip resurfacing, both implant types enable the same level of physical activity. These activity levels depend on individual lifestyle choices rather than on implant type. Outcomes of revision procedures are not worse in patients with a metal-on-metal-hip arthroplasty: high revision and re-revision rates were found, but these rates are comparable and even lower than in patients with non-metal-on-metal arthroplasty. It was demonstrated that patient-reported outcome measures are of limited use for assessing physical activity levels. Patient-reported outcome measures hardly capture differences in activity that can be objectively measured with a wearable activity monitor.

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Chapter X

Valorisation

Persistence can change failure into extraordinary achievement

(Marv Levy)

This paragraph describes how the knowledge acquired in the reserach for this thesis can be made available for economic and social utilization.

The litature concerning results of metal-on-metal (MoM) hip arthroplasty, both large head metal-on-metal (LHMoM) total hip arthroplasty (THA) and hip resurfacing arthroplasty (HRA), showed how expectations turn out to be different. A discrepancy between the expected advantages and the long-term patient related outcomes in clinical practice is observed. The theoretical advantages were presented as the new 'big thing' in hip arthroplasty. Money-driven strategies with patient-attraction magnets ('sportship') were only beneficial for investors and developers of HRA. Unfortunately, the sales talk and news spread faster than the acquisiton of postoperative results, the disadvantages of HRA only became clear after hundreds of thousands of patients had already been operated. The influence of industries, e.g. by direct mailing to patients to make a connection to the 'consumers', and of health care insurance companies should not be underestimated. In 2012, the NetherlandsOrthopaedicAssociation (NOV) advised against the use of any MoM hip arthroplasty [1]. Hereafter, the use of hip arthroplasties with a MoM articulation decreased. The Dutch Arthroplasty Register (LROI) data showed that MoM was used in 5.2% of THA cases in 2010, 1.51% in 2012 and 0.02% to 0.12% between2014 and 2019 [2]. Interestingly and in contrast to the advice of the NOV, health care insurances provided patients with opportunities to travel abroad for HRA procedures. The financial incentive seemed more important than protecting and informing patients.

Orthopaedic surgeons are obligated to inform patients about both conservative and operative therapies according to the Hippocratic Oath [3]. A decision for treatment is ideally based on a shared-decision process. For surgeons, it is easier to perform a hip arthroplasty than to convince and support patients to lose weight and increase their physical activity. Currently, there is too little attention for preventive medicine. Prevention of overweight, smoking and inactivity is not stimulated enough and should start as early as possible, preferably in primary school. In the current situation, opting for a surgical intervention is easier for both the patient and the surgeon. In the training of orthopaedic residents, this temptation should be addressed with more urgency. Communication skills and recognizing the right indication for surgery are equally important as surgical skills. As residents have numerous 'general tasks' and their training is divided into stages (e.g. hip, knee, spine, trauma), it can be difficult to follow a patient over time. However, it is highly important for a resident to follow a patient during the postoperative phase after indicating the patients for surgery, so that postoperative results can be used as feedback. Of course, this

also applies to conservative treatment. In addition, conducting scientific research leads to developing a critical view and, among other things, improves planning and organizational skills.

The introduction of new orthopaedic implants should be phased and evidence-based, none of which was the case in the introduction of MoM hip arthroplasty. A decent pre-market setting to detect early failure modes would have shown the increased risk of femoral neck fractures. Also, with careful thinking in combination with in-vitro testing, wear of the articulating surfaces and release of metal ions could have been predicted. New designs of HRA are developed and implanted in the context of clinical research, e.g. HRA with a cobalt-chromium femoral component and cementless acetabular cups with a cross-linked ultra-high molecular weight polyethyelene (XLPE)-acetabular liner and with a ceramic-on-ceramic (CoC) bearing [4, 5].

A phased and evidence-based introduction should not only consider subjective outcomes, such as clinically administered tools and patient-reported outcome measures (PROMs); as the present research has demonstrated, it is highly valuable to include objective measures, such as wearable activity monitors, to obtain objective data on physical activity in daily living. The new designs of HRA described above should be subject to meticulous clinical research. Physical activity should be measured objectively both pre- and postoperatively in these patients and should be compared with physical activity measurements of patients who received conventional stemmed THA. In this way, the theoretical advantages of HRA could be evaluated on objective grounds. Before new materials and techniques are investigated, there must first be a clear understanding of the problem of the existing technique that needs to be solved.

Physical activity monitoring, with the use of wearable monitors, could be used in a wide spectrum, both in clinical settings and in research. This thesis showed that PROMs hardly capture the intensity levels and behavioral differences that can be objectively measured by monitoring physical activities of daily living. PROMs are increasingly used to assess pain and physical function and to serve as indicators of outcome quality in national joint registries, but the true functional recovery after joint arthroplasty can be better determined with objective outcome assessment, such as wearable activity monitoring. There is ample evidence of the importance of physical inactivity as a major risk factor for a number of adverse health outcomes. Wearable activity monitors may be used in cardiovascular, neurodegenerative and orthopaedic patient populations. Also, the geriatric patient population might

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benefit from activity monitoring as a wearable fall detection system in daily living. Often, falls and related injuries mark the onset of deterioration of health [6].

The long-term follow-up of patients after hip arthroplasty is questionable. In prostheses with known excellent long-term clinical results, especially those validated by joint registry studies, follow-up could be modified. Routine follow-up of asymptomatic patients after hip arthroplasty may be highly costly and perhaps unnecessary. Other, less intensive review methods might be more appropriate, such as objective physical activity monitoring with wearables. With the recent improvements of the capabilities of smartphones and smartwatches, these appliances could be useful in the follow-up of patients after total joint arthroplasty. Applications can support and guide patients and can deliver data and patient reported feedback to facilitate improved care, outcomes and satisfaction. Physical activity tracking is available, but it is not yet as complete as the wearable activity monitoring used in the present thesis. However, a smartphone is a more accesible platform with 93% of the Dutch population owning a smarthphone. Various patient-proof applications are already widely available. Apps were developed to inform the patients about their pre-, peri- and postoperative phase and to obtain information regarding their activites. The use of smartphone applications is highly interesting for patient monitoring at a distance and for putting the patient in control of their own rehabilitation, for instance after a hip arthroplasty. Issues may arise about data ownership, since this information may offer a source of profit both for industries and health insurances. Current laws lack specific regulation. Another option might be the use of smart hip implants, which have been available since 1966 and have been used to measure pressure, forces, strain, displacement, temperature and physical paramaters from inside the body. However, smart implants have only been used in research and have not yet become a part of daily clinical practice. With the rapid advance of technology, it seems that the widespread implementation of smart implants is near and will potentially affect clinical care and enable personalized medicine [7]. It is, however, questionable if that makes sense for smart implants in or with THA; they are probably mainly usefull in clinical research.

After MoM hip arthroplasty, patients should be routinely monitored. Those with a painful hip will find their way to the outpatient clinic. In all other cases, monitoring should focus on the general symptoms of chronically raised metal ion concentrations as described in this thesis. At this moment, it is still unclear what the effects of chronically elevated metal ion concentrations are (unexpected failures at the post-market phase). Ideally, these effects should be investigated with a validated questionnaire, followed by referral to a specialist (ophthalmologist, ENT

doctor, neurologist, cardiologist, internal physician, toxicologist), determination of blood metal ion concentrations and, if necessary, explantation or revision of the MoM hip. Orthopaedic surgeons all around the world decided to implant this type of hip arthroplasty without knowing the potential side effects. It is our responsibility, in cooperation with the implant industry, to support these patients where possible.

This thesis underscores the importance of training medical specialists in independent thinking, of doing the appropriate research before introducing new techniques and materials, and of carefully examining the clinical processes and not taking for granted what is suggested by others.

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Chapter XI

Summary

Good is not good when better is expected
(Vin Scully)

Worldwide, hip arthroplasty is increasingly performed as treatment for end-stage osteoarthritis. The operation is one of the most successful procedures in the history of healthcare. Improvement of outcomes after these surgeries is not solely based on the theoretical advantages of this surgical procedure itself. Since the start of hip arthroplasty (1821) all modifications on the design of the prosthesis, including the development of new materials, the surgical approach, fixation techniques and bearing surfaces, were implemented because of their theoretical advantages. In the early 2000s, the worldwide popularity of metal-on-metal (MoM) total hip arthroplasty (THA), both large-head THA (LHMoM) and hip resurfacing (HRA) was at its peak. HRA had, at least in theory, various advantages compared to conventional stemmed THA with a metal-on-polyethylene (MoP) bearing, such as low volumetric wear, femoral heads with a large physiological diameter offering stability, near-natural joint kinematics, a greater range of motion than THA with a small femoral head diameter, and preservation of the femoral bone, which would permit an easy revision if needed. The introduction of this thesis describes the history and development of hip arthroplasty from 1821 up to the early 2000s. Concerns about MoM hip arthroplasty have been raised since 2004 due to the reported high failure rates and the discovery that all patients with a MoM hip prosthesis have raised blood/serum metal ion concentrations of cobalt and chromium after implantation. These concentrations are used as a surrogate marker of in-vivo wear and are influenced by a variety of parameters, both patient-, implant- and surgery-related factors. The influence of physical activity (PA) is unknown, while in theory, the daily habitual PA of patients with a MoM hip arthroplasty could be associated with metal ion concentrations in blood. MoM hip arthroplasty was mainly offered to younger patients, who tend to have higher demands on functional outcomes. Outcome measures after THA can be assessed in multiple ways and by different judgements, i.e., by the clinician and by the patient, but disagreement between them was shown. Patient-reported outcome measures (PROMs) relate to the patients' beliefs and experiences regarding their functional ability, while objective PA monitoring with the use of a wearable activity monitor (AM) proves what a patient actually does in activities of daily life. The introduction outlines the aims of this thesis and the research questions:

- What is the relation between objectively measured physical activity and blood metal ion concentrations in patients with a metal-on-metal hip arthroplasty?
- Are patients with an HRA physically more active than patients with a conventional stemmed THA?
- Is objectively measured physical activity associated with patient-reported physical activity?

- Is the outcome of revision surgery after failed MoM hip arthroplasties worse than the outcome of revision after failed non-MoM hip arthroplasties?
- Are chronically raised metal ion concentrations in blood associated with systemic complaints?

In this thesis, PA in daily life was measured during the waking hours of four consecutive days using a commercially available AM with a 3-axis accelerometer, gyroscope and magnetometer, attached to the leg. The relation between objectively measured PA and blood metal ion concentrations was described in chapter II. In a cohort-study (n=62), metal ion concentrations were determined using inductively coupled plasma mass spectrometry (ICP-MS), and habitual PA of subjects was measured in daily living with an AM. Subgroups with low cobalt ion concentrations (<40 nmol/L) and high cobalt ion concentrations (>40 nmol/L) were compared. The results showed that cobalt ion concentrations were highly elevated overall at follow-up after more than 6 years. None of the PA parameters showed any correlation with cobalt ion concentrations, and in addition, the subgroup analysis showed no significant differences in terms of PA. The daily step count in this study was comparable to that of healthy people of the same age, showing that this population with a MoM prosthesis is normally active and that MoM hip arthroplasty does not limit patients with regard to habitual walking activities.

A major concern in the first study was the heterogeneity of prostheses included and the follow-up since surgery. An attempt was made to solve this issue in the next study, which is described in chapter III. In a more homogenous cohort (n=16) of patients with a unilateral HRA, PA and blood metal ion concentrations were determined at 10-year follow-up. The study aimed to uncover an important contributor that might previously have been overlooked. The cohort showed a wide range in cobalt ion concentrations. A significant and clinically meaningful correlation was found between higher cobalt ion concentrations and two distinct parameters of habitual PA: a higher number of sit-standtransfers (SST) and high-intensity peaks. No significant association was found between cobalt ion concentrations and the habitual level of time spent walking, the total number of steps, or the percentage of time being active. It seems that metal ion concentrations are not or only slightly influenced by general habitual PA, such as normal walking. The only aspects of PA that matter are behavioral (many STT) and qualitative (high intensity, fast walking). For patients, it seems safe to engage in activities with low-intensity peaks, such as walking or cycling without triggering critical wear or metal ion release, which enables them to achieve important general health benefits and quality of life.

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It can be expected that patients who received an HRA would be more physically active after surgery than patients who received a stemmed THA with a small-diameter metal-on-polyethyelene (MoP) or ceramic-on-polyethylene (CoP) bearing. This expectation is based on multiple reasons: the theoretically better implant design features, which claim to support a more active lifestyle, the selection of patients for this particular implant (young and active), and the related patient expectations (high preoperative demands on postoperative activity). To objectify if patients with an HRA are more physically active, a study was performed as described in chapter IV: objective PA at long term follow-up (10-years) was determined in a cohort of 16 HRA and 16 stemmed THA subjects matched for sex, age at surgery, follow-up since surgery, and BMI. Group characteristics did not differ statistically at baseline. Contrary to expectations, results showed that patients with a unilateral HRA were not more physically active. In the stemmed THA group, two factors established to be related with a less active lifestyle were higher: the median age (difference: $\pm$ 4 years) and BMI (difference: $\pm$ 3 kg/m^2), but these differences were not statistically significant. HRA patients do not seem to be more physically active; both implant types enable the same level of PA, and activity levels depend on individual lifestyle rather than on implant type, at least at 10-year follow-up. Even well-reasoned theoretical advantages concerning functionality of any implant design require clinical validation and should not be assumed as an indication, especially at the risk of a potential disadvantage.

The reliability of PROMs can be hampered by their subjective nature, recall bias, ceiling effects, low response andcompletion rates or transcription errors, and by the fact that it is a time-consuming method. There is no hard evidence in current literature how objectively measured PA is related to patient-reported PA. Chapter V describes a study on the correlation of PROMs of general health (SF-36), disease-specific outcome and physical function (HOOS-PS), joint-awareness (FJS-12) and self-perceived activity levels (SQUASH) with objectively measured PA parameters. This study included the same cohort (n=32) that was also used in the study described in the previous chapter (IV). The main finding was that objectively measured PA levels (time walking, total time active, number of steps) did not show a correlation with the FJS-12 and SQUASH, but did show a significant correlation with the HOOS-PS and the physical functioning subscale of the SF-36. The correlations found were of moderate strength (Pearson's r 0.40-0.59).The association between objectively measured PA and PROMs is limited: this study shows that PROMs are hardly affected by or do hardly capture levels and differences in objectively measured PA, which is a supposedly patient-centred outcome and a goal of THA. Objectively measured PA, assessed with a wearable AM, and PROMs should be considered complementary, and both should be used in clinical practice.

Some literature suggested that the outcome of revision surgery in failed MoM hip arthoplasties is moderate, especially when revision was performed due to an adverse reaction to metal debris (ARMD). To determine whether this suggestion is valid, the preferred type of research is a large database study. National joint replacement registries are multi-centre databases comprising data on thousands of subjects and implants, which allows for identifying variables predictive of implant failure. The Dutch Arthroplasty Register (LROI) has a coverage of 100% and a completeness >95%. LROI data was used to determine the outcome of revision of a failed MoM hip arthroplasty and to compare this outcome to the outcome of revised failed non-MoM hip arthroplasties. Results are reported in Chapter VI. Records were excluded if the reason for index revision was infection. A total of 3.478 records of revised implants were included, 873 of which were MoM-implants (25.1%). Over the course of follow-up, 12% of MoM implants were re-revised, at a median follow-up of 5 years. The re-revision rate of non-MoM THA was 14% at 5-year follow-up. Statistically significant risk factors for re-revision of failed MoM implants were a periprosthetic fracture as reason for index revision (HR 1.98), a MoM articulation after the index revision (HR 2.48), and femoral-only revisions (HR 3.20). A symptomatic MoM bearing as reason for index revision (HR 0.53) was found to be a statistically significant factor for reducing the probability of re-revision. This success may have been helped by patient characteristics such as minimal bone loss and a good bone stock. Revision surgery in failed MoM hip arthroplasties has a high risk of re-revision, but this risk is comparable to and even lower than the risk of re-revision in non-MoM hip arthroplasties. Femoral-only revisions and MoM articulations post-revision should not be used in revision of a failed MoM hip arthroplasty. The outcomes of this study can behelpful in managing the expectations of patients and orthopaedic surgeons regarding the outcomes of re-revisions.

After the implantation of a MoM hip arthroplasty, an increase is seen in metal ion levels in blood serum, which is due to the release of ions from the metal surface, directly and even more so during articulation, and to corrosion of the bearing surfaces. Patients should be identified prior to experiencing systemic symptoms, although it is unknown whether chronically raised metal ion concentrations are associated with systemic complaints. An increasingly described complication with severe systemic symptoms and sometimes even leading to mortality is cobalt intoxication. A chronically raised cobalt ion concentration may result in a variety of symptoms and lead to toxicity, which is known as 'Prosthetic Hip-Associated Cobalt Toxicity (PHACT)'. The next study of this thesis aimed to elucidate whether symptoms are associated with cobalt ion concentrations in blood. Chapter VII described the outcomes of a systematic review of cobalt toxicity case reports to

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identify the systematic symptoms described most frequently and to determine the toxicity threshold level of serum cobalt ion concentration. Of a total of 7645 identified references, 67 relevant reports were included describing 79 patients. Risk of bias was classified as low (Newcastle-Ottawa Scale; 98.5%, N = 66), and methodological quality was rated as good (Murad et al.; 76.1%, N = 51). A primary MoM bearing was used in 38 cases (48%) and in 31 cases (39%), a metal component was used in the revision of a fractured ceramic component. Of all the described symptoms, most were seen in the sensory system (24%), followed by the cardiovascular system (22%) and the neurological system (19%). The calculated individual serum cobalt ion threshold for MoM was 123.7 (± 96.8) ppb and 1078.2 (± 1267.5) ppb for CoC bearings. Since many MoM bearings are still in situ, more PHACT cases can be expected. Unfortunately, the cobalt ion concentration varied widely between all reports, hence no clear toxicity threshold could be extracted from these case studies.

Chapter VIII describes a cohort study (n=62) investigating the self-reported systemic complaints of patients with a MoM hip arthroplasty at different cobalt ion concentration thresholds (120, 170 or 220 nmol/L). The results demonstrated that ocular-vestibular symptoms were more common in high cobalt ion concentration groups for the three threshold levels tested and that the prevalence increased at higher threshold values. This finding suggests a correlation between cobalt ion concentration and symptom prevalence. With regard to proactively requested, self-reported symptoms, the threshold at which effects may be present could be lower than the cobalt ion concentration values that are currently applied in clinical follow-up.

Chapter IX (general discussion) discussed the main findings of this PhD-thesis in a broader perspective. Clinical implications and suggestions for further research are described. Chapter X on valorisation describes how the knowledge acquired in the research for this thesis can be made available for economic and social utilization.

Final remarks

This thesis showed the possibilities of using wearable physical activity monitors in the daily practice of patients with a hip arthroplasty. The use of wearable activity monitors in the present research demonstrated that moderate habitual physical activity, such as normal walking, only slightly influences serum metal ion concentrations (as an indirect measure of wear). On the other hand, higher serum metal ion concentrations were associated with a higher number of sit-stand transfers (SST) and high-intensity peaks in patients with a metal-on-metal hip arthroplasty. Despite the subjective nature of patient-reported outcomes, their

potential value in current practice is shown, for example in determining systemic complaints due to chronically raised cobalt ion concentrations. Theoretically better implant design features are not necessarily also superior in practice. For all new types of implants, a phased evidence-based introduction is highly mandatory. This advice also applies to new designs of HRA: thorough clinical research should be performed, especially concerning objectively measured physical activity, both pre- and postoperatively, in patients with these new designs of HRA in comparison with conventional stemmed THA. In this way, the theoretical advantages of HRA could be determined on objective grounds.

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Chapter XII

Samenvatting

If you fail to prepare, you're prepared to fail
(Matt Biondi)

Een totale heup prothese (THP) wordt wereldwijd in toenemende mate geplaatst, voornamelijk als behandeling voor het eindstadium van artrose. De operatie wordt beschouwd als één van de meest succesvolle in de historie van de gezondheidszorg. Sinds het begin van chirurgische ingrepen aan het heupgewricht (1821) zijn er vele modificaties gedaan aan de procedure: de ontwikkeling van nieuwe materialen, de chirurgische benadering, de fixatie technieken en de articulerende contact oppervlakten. De populariteit van metaal-op-metaal (MoM) heupprothesen was op zijn top begin 2000, zowel voor de grote-kop MoM THP, Large Head Metal on Metal (LHMoM), als voor de heup resurfacing artroplastiek (HRA). De HRA had vergeleken met de conventionele gesteelde THP met een metaal-op-polyethyleen (MoP) articulerend contact oppervlak verschillende theoretische voordelen: minder slijtage, meer stabiliteit, een natuurlijkere gewrichtskinematica en een groter bewegingsbereik vergeleken met een THP met een kleine heupkop. Indien nodig zou een revisie gemakkelijker zijn en de resultaten beter omdat het proximale femur grotendeels behouden blijft bij een resurfacing heup artroplastiek.

De introductie van dit proefschrift beschrijft de historische ontwikkelingen van het kunstheupgewricht sinds 1821 tot het begin van de jaren 2000. In 2004 ontstond bezorgdheid over de MoM prothesen vanwege het hoge faal percentage. Daarnaast vond men dat patiënten met een MoM prothese verhoogde metaalconcentraties in het bloed hadden. Deze bloedwaarden kunnen gebruikt worden om de mate van slijtage van de metaal oppervlakten aan te tonen. Zij worden beïnvloed door verschillende factoren: de patiënt, het implantaat en de operatietechniek. In theorie bestaat er een directe relatie tussen de dagelijkse fysieke activiteiten van patiënten met een MoM heupprothese en de hoogte van de metaalconcentraties in het bloed. Deze theorie is tot op heden echter niet bevestigd. Vooral bij jongere patiënten werd een MoM heupprothese aangeboden, die op hun beurt hoge verwachtingen hadden op het gebied van functionele uitkomsten. Deze uitkomsten na een THP kunnen zowel door de dokter als door de patiënt worden beoordeeld. Zij verschillen echter vaak in hun beoordelingen van elkaar. Hierbij kan gebruik worden gemaakt van vragenlijsten en van meetinstrumenten die activiteiten registreren. Patiënt gerapporteerde uitkomstmaten met vragenlijsten (Patient Reported Outcome Measures, PROMs) hebben betrekking op de ervaring van de patiënt en zijn of haar functionele mogelijkheden. De monitoring van de fysieke activiteit (FA) van een patiënt door gebruik van een (draagbare) activiteitenmonitor (AM) registreert wat een patiënt daadwerkelijk doet qua activiteiten in het dagelijks leven. In Hoofdstuk I worden de doelstellingen en de onderzoeksvragen van dit proefschrift besproken:

- Wat is de relatie tussen objectief gemeten fysieke activiteit en metaal concentraties in het bloed, bij patiënten met een metaal-op-metaal heupprothese?
- Zijn patiënten met een resurfacing heup artroplastiek fysiek actiever in vergelijking met patiënten met een conventionele totale heup prothese?
- Is objectief gemeten fysieke activiteit van patiënten met een heupprothese in overeenstemming met de uitkomsten van patiënt gerapporteerde fysieke activiteit?
- Is de uitkomst van revisie chirurgie bij patiënten met een gefaalde MoM heupprothese slechter in vergelijking met revisie chirurgie bij een gefaalde niet-MoM heupprothese?
- Zijn chronisch verhoogde metaal concentraties in het bloed als gevolg van een MoM heupprothese geassocieerd met systemische klachten?

Voor dit proefschrift werd gebruik gemaakt van een commercieel verkrijgbare activiteitenmonitor met een versnellingsmeter, gyroscoop en magnetometer in drie richtingen (X-, Y- en Z-as). De AM werd op het been geplakt om de FA gedurende vier dagen te meten. De relatie tussen objectief gemeten fysieke activiteit en de metaalconcentraties in het bloed bij patiënten met een MoM heupprothese zijn beschreven in hoofdstuk II. In een cohort studie (n=62) werden de metaalconcentraties in het bloed bepaald middels 'inductively coupled plasma mass spectrometry (ICP-MS)'en de dagelijkse fysieke activiteit met behulp van de activiteitenmonitor. De resultaten toonden aan dat de gemiddelde kobalt concentraties fors verhoogd waren, ook na meer dan 6 jaar postoperatief. Een subgroep analyse werd verricht tussen een groep met lage kobalt concentraties in het bloed (<40 nmol/L) en een groep met hoge kobalt concentraties (>40 nmol/l). Geen enkele van de fysieke activiteiten parameters toonde een correlatie met de kobaltconcentraties. Ook de subgroep analyse toonde geen significante verschillen tussen de groepen aan. Het gemiddeld aantal stappen per dag van de patiënten in deze studie was vergelijkbaar met gezonde proefpersonen van dezelfde leeftijd. Dit duidt op een normaal activiteitniveau van de patiënten populatie in deze studie. Tevens voelen patiënten met een MoM heupprothese zich niet beperkt in dagelijkse fysieke activiteiten. Een belangrijke beperking van deze studie was dat deze werd uitgevoerd met een heterogene patiënten populatie. Patiënten met zowel een unilaterale en/of bilaterale prothese maar ook met beide typen MoM heupprothesen (HRA en/of LHMoM) werden geïncludeerd.

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In een volgende studie werd getracht om deze heterogeniteit er uit te filteren, de resultaten worden beschreven in Hoofdstuk III. Een meer homogeen cohort (n=16) van patiënten met een unilaterale HRA 10 jaar postoperatief werd samengesteld. De fysieke activiteit werd gemeten en de kobalt concentratie in het bloed werd bepaald op de eerste dag. Het doel van deze studie was om fysieke activiteit als een belangrijke verklaring te vinden voor verhoogde kobalt concentraties. Er was sprake van een grote spreiding in de kobalt concentraties van de patiënten. Er werd een significante correlatie gevonden tussen de kobalt concentraties en verschillende parameters van dagelijkse fysieke activiteit (aantal zit-sta-transfers en hoge-intensiteit pieken). Er werden geen statistisch significante verbanden gevonden tussen kobalt concentraties en de dagelijkse tijd besteed aan wandelen, het totaal aantal stappen en het totaal percentage van de tijd dat men fysiek actief was. Het lijkt erop dat de kwantitatieve algemene dagelijkse activiteiten, zoals normaal wandelen, de kobalt concentraties niet of slechts in geringe mate beïnvloeden. Vooral kwalitatieve aspecten van de activiteiten (hoge intensiteit, snel wandelen, veel zit-sta transfers) lijken invloed te hebben op de kobalt concentraties. Het lijkt veilig voor patiënten met een MoM heupprothese om te participeren in activiteiten met een lage intensiteit, zoals wandelen en fietsen. Hierdoor ontstaat geen ernstige slijtage van de articulerende contact oppervlakten en worden er geen hoge metaalconcentraties veroorzaakt.

Om meerdere redenen is het logisch om te veronderstellen dat patiënten met een HRA meer fysieke activiteit vertonen dan patiënten met een conventioneel gesteelde THP met een metaal-op-polyethyleen (MoP) of keramisch-op-polyethyleen (CoP) articulerende contact oppervlakten: op basis van het theoretische veronderstelde betere design van de HRA werd de mogelijkheid van een actievere levensstijl gepromoot. Hierdoor was de selectie van patiënten voor dit type implantaat (jong en actief) en van hun verwachtingen (hoge preoperatieve verwachtingen van de postoperatieve activiteit) anders dan bij een conventionele gesteelde THP. Of patiënten met een HRA daadwerkelijk fysiek actiever waren werd onderzocht. Deze studie wordt beschreven in hoofdstuk IV van dit proefschrift: de objectieve fysieke activiteit na een lange termijn follow-up (10 jaar) werd bepaald voor een geslacht-, leeftijd bij operatie-, follow-up sinds operatie-, en BMI- vergelijkbaar cohort van HRA patiënten en van patiënten met een conventionele gesteelde THP. De groepen waren homogeen, er waren geen statistisch significante verschillen tussen de groepen bij aanvang van de studie. In tegenstelling tot de verwachtingen bleken de patiënten met een HRA niet fysiek actiever te zijn. Patiënten vertonen vergelijkbare fysieke activiteiten onafhankelijk van het type implantaat. De mate van fysieke activiteit lijkt meer afhankelijk te zijn van de individuele levensstijl dan van het

type prothese, tenminste 10-jaar na de operatie. Dit laat nog eens zien dat zelfs goed onderbouwde theoretische voordelen van een implantaat klinische validatie vereisen en niet zondermeer als voordeel mogen worden beschouwd.

De validiteit van PROMs is beperkt door het subjectieve karakter, verstoring van de resultaten omdat patiënten zich bepaalde zaken anders herinneren dan de manier waarop ze in werkelijkheid gebeurt zijn, plafondeffecten, de tijdrovende methodologie, het lage respons- en voltooiing percentage en/ of transcriptiefouten. Tot op heden was er geen literatuur beschikbaar die objectief gemeten fysieke activiteit relateert aan patiënt gerapporteerde fysieke activiteit. In Hoofdstuk V wordt een studie beschreven waarin PROMs ten aanzien van de algemene gezondheid (SF-36), de ziektespecifieke uitkomsten en het fysiek functioneren (HOOS-PS), het gewrichtsbewustzijn (FJS-12) en het zelf-waargenomen activiteitenniveau (SQUASH) worden gecorreleerd aan objectief gemeten activiteiten. Dit patiëntencohort (n=32) werd ook gebruikt in het vorige hoofdstuk (IV). De belangrijkste bevinding van deze studie was dat verschillende objectief gemeten fysieke activiteit parameters (wandeltijd, totale actieve tijd en het aantal stappen per dag) geen correlatie toonden met de FJS-12 en de SQUASH. Er werd wel een statistisch significante correlatie gevonden met de HOOS-PS en de subschaal 'fysiek functioneren' van de SF-36. De gevonden correlaties waren van matige sterkte (Pearson's r 0.40-0.59). Deze studie liet zien dat PROMs nauwelijks overeenkomen met de objectief gemeten fysieke activiteit. De objectief gemeten fysieke activiteit, bijvoorbeeld door middel van een draagbare activiteitenmonitor, en PROMs moeten als complementair worden beschouwd en kunnen beide een rol spelen in de klinische praktijk.

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In de literatuur wordt gesuggereerd dat de uitkomsten van revisie chirurgie van een gefaalde MoM heupprothese matig is, in het bijzonder wanneer de revisie is uitgevoerd in verband met locale reacties op metaalpartikels, 'adverse reactions to metal debris' (ARMD). Door middel van grote database studies kunnen deze suggesties onderzocht worden. Nationale registers voor gewrichtsvervanging zijn multicenter databases met gegevens van duizenden patiënten. Dit maakt het mogelijk om variabelen te identificeren die een voorspellende waarde kunnen hebben voor het falen van een implantaat. De Nederlandse Landelijke Registratie Orthopedische Implantaten (LROI) van de Nederlandse Orthopedische Vereniging (NOV) heeft een dekking van 100% en een volledigheid van >95%. LROI-gegevens werden gebruikt om de resultaten van revisies van MoM heupprothesen te vergelijken met revisies van niet-MoM heupprothesen. De resultaten van deze studie worden gerapporteerd in hoofdstuk VI. Alle eerste revisie ingrepen die

werden uitgevoerd in verband met een infectie, werden geëxcludeerd voor dit onderzoek. In totaal werden 3.478 gereviseerde heupimplantaten onderzocht, waarvan 873 (25.1%) MoM-implantaten. Gedurende de follow-up onderging 12% van de primaire MoM-implantaten een re-revisie, dit bleek 14% te zijn voor de niet-MoM prothesen, bij een mediane follow-up duur van 5 jaar. Het regressiemodel liet zien dat voor MoM-implantaten een periprothetische fractuur als reden voor de eerste revisie (hazard ratio (HR)1.98), een MoM-articulatie na de eerste revisie (HR 2.48) en een partiële revisie van de steel (HR 3.20) statistisch significante risicofactoren waren voor een re-revisie. Een symptomatische MoM heupprothese, zonder aanwijzingen voor een fractuur of loslating, als reden voor de eerste revisie (HR 0.53) bleek een statistisch significante verkleinende factor voor de kans op re-revisie. De uitkomsten wijzen op een degelijke chirurgische ervaring in Nederland voor dit soort revisies, mogelijk bijgedragen door patiëntkenmerken zoals minimaal botverlies en een goede botvoorraad. Revisiechirurgie bij gefaalde MoM heupprothesen heeft een hoog risico op re-revisies, maar dit is vergelijkbaar met de uitkomst van revisies bij niet-MoM heupprothesen. Een partiële revisie van de steel en een MoM-articulatie na de eerste revisie laten slechte resultaten zien in de chirurgische behandeling van een gefaalde MoM heupprothese. De resultaten van deze studie kunnen bruikbaar zijn bij het managen van de verwachtingen van patiënten en orthopedisch chirurgen.

Na de implantatie van een MoM heupprothese wordt bij patiënten een stijging gezien in metaal concentraties in het bloed en serum door directe afgifte van het metalen oppervlak. Kobalt intoxicatie is een steeds vaker beschreven complicatie met potentieel ernstige symptomen, mogelijk met de dood tot gevolg. Idealiter zouden patiënten voordat een intoxicatie ontstaat al geïdentificeerd zijn. Het is echter onduidelijk of en hoe chronisch verhoogde metaal concentraties geassocieerd zijn met systemische afwijkingen en symptomen. Deze symptomatologie kan leiden tot een beeld dat bekend is als 'Prosthetic Hip-Associated Cobalt Toxicity (PHACT)'. Welke symptomen geassocieerd zijn met kobalt concentraties in het bloed, werd onderzocht in Hoofdstuk VII. Dit hoofdstuk beschrijft een systematische review van case reports betreffende kobalt intoxicaties om te bepalen welke systemische klachten het meest voorkomen. Aanvullend doel was om een kobalt drempelwaarde te bepalen waarboven klachten ontstaan. In totaal werden 7.645 referenties gevonden waarvan er 67 overbleven na exclusie. Deze artikelen beschreven gezamenlijk 79 patiënten. Het risico op een systematische fout in onder meer de analyse, de resultaten of de conclusies van een onderzoek werd in deze analyse als laag geclassificeerd (Newcastle-Ottawa Scale; 98.5%, N = 66), bij een goede methodologische kwaliteit (Murad et al.; 76.1%, N =

51). Een primaire MoM articulatie werd in 38 (48%) patiënten gebruikt, bij 31 (39%) patiënten werd een metalen component gebruikt bij de revisie van een gebroken keramische component. De oorsprong van de meeste symptomen lag in het sensorische systeem (n=77, 24%), gevolgd door het cardiovasculaire(n=71, 22%) en neurologische systeem (n=62, 19%). De berekende individuele drempelwaarde voor MoM prothesen was 123.7 (± 96.8) parts per billion (ppb) en 1078.2 (± 1267.5) ppb voor CoC-contact oppervlakten. Omdat er nog vele patiënten met een MoM heupprothese zijn, kunnen er in de toekomst meer patiënten met kobalt gerelateerde systemische klachten verwacht worden. De drempelwaarde van kobalt, waarbij klachten zich gaan manifesteren, kon niet worden bepaald door de sterke spreiding van de beschreven concentraties.

Aanvullend op de systematische review wordt in hoofdstuk VIII een cohort studie (n=62) beschreven naar de zelfgerapporteerde systemische klachten bij patiënten met een MoM heupprothese. Het optreden van deze symptomen werd bepaald bij verschillende drempelwaarden van kobalt in het bloed (120, 170 of 220 nmol/L). De resultaten toonden aan dat oculo-vestibulaire symptomen vaker voorkwamen in de groepen met een hoge kobalt concentratie en met toenemende prevalentie voor hogere drempelwaarden. Dit is een aanwijzing voor de correlatie tussen kobalt concentratie en symptoomprevalentie. Met betrekking tot proactief onderzochte, zelfgerapporteerde symptomen zou de drempelwaarde waarbij klachten aanwezig zijn, lager kunnen zijn dan de waarden die momenteel worden gehanteerd tijdens de klinische follow-up.

In Hoofdstuk IX (general discussion) worden de belangrijkste bevindingen van dit proefschrift in een breder perspectief besproken. Klinische implicaties en suggesties voor verder onderzoek komen hier aan bod. Hoofdstuk X (valorisation) beschrijft hoe de kennis opgedaan in dit proefschrift toegepast kan worden in de maatschappij.

Dit proefschrift beschrijft een mogelijkheid voor het gebruik van draagbare fysieke activiteitenmonitoren in de dagelijkse praktijk. Algemene dagelijkse activiteit, zoals lopen, heeft slechts een geringe invloed op metaal concentraties in het bloed bij patiënten met een metaal-op-metaal heupprothese. Anderzijds zijn kwalitatieve aspecten van fysieke activiteit wel van belang bij deze patiënten. De subjectieve aard van patiënt gerapporteerde uitkomsten wordt geschetst, maar hun waarde wordt ook getoond in de huidige praktijk, bijvoorbeeld bij het vaststellen van systemische klachten als gevolg van chronisch verhoogde kobalt concentraties. Een theoretisch onderbouwt beter ontwerp van een implantaat is niet per definitie beter in de

praktijk. Een gefaseerde, op bewijs gebaseerde introductie is van groot belang voor alle nieuwe implantaten. Dit geldt ook voor nieuwe ontwerpen van de resurfacing artroplastiek. Ethisch en methodologisch onderbouwd klinisch onderzoek moet worden uitgevoerd bij patiënten met deze nieuwe implantaten. Met betrekking tot objectief gemeten fysieke activiteit zou het de voorkeur hebben om patiënten met nieuw ontwikkelde gewrichtsprothesen zowel pre- en postoperatief te monitoren. Op deze manier kunnen de theoretische voordelen objectieve gronden worden bepaald.

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List of Publications

Always make a total effort, even when the odds are against you

(Arnold Palmer)

This thesis
Metal ion concentrations after metal-on-metal hip arthroplasty are not correlated with habitual physical activity
Jelsma J, Schotanus M, Senden R, Heyligers IC, Grimm B
Hip Int. 2019 Nov;29(6):638-646.

Quality, but not quantity of physical activity is associated with metal ion concentrations in unilateral hip resurfacing
Jelsma J, Schotanus MGM, van Kuijk SMJ, Buil I, Heyligers IC, Grimm B.
J Orthop Res. 2020 Feb 22.

Patients with hip resurfacing arthroplasty are not physically more active than those with a stemmed total hip
Jelsma J, Schotanus MGM, Buil ITAF, van Kuijk SMJ, Heyligers IC, Grimm B.
Acta Orthop . 2020 Jun 4;1-5

Only limited correlations between patient-reported outcomes and objectively monitored physical activity 10-years after THA
Jelsma J, van Kuik S, Buil I, Heyligers I, Grimm B, Schotanus M
Accepted in: Acta Orthop Belg on 06.06.2021

Outcome of Revised Metal-on-Metal Hip Arthroplasties: a Dutch Arthroplasty Register Study
Jelsma J, van Kuijk S, Spekenbrink-Spooren A, Grimm B, Heyligers I, Schotanus M
Accepted in: Arch Orthop Trauma Surg on 12.11.2021

Prosthetic hip associated cobalt toxicity: a systematic review of case series and case reports
Crutsen JRWA, Koper MCA, Jelsma J, Heymans M, Heyligers IC, Grimm G, Mathijssen NMC, Schotanus MGM
Revision submitted to: EFORT Open Reviews on 12.12.2021

Self-reported systemic complaints in patients with metal-on-metal hip arthroplasty
Jelsma J, Schotanus M, Kleinveld H, Grimm B, Heyligers IC.
J Orthop. 2020 Jan 25;18:213-217

Other publications

- **Zwelling van het bovenbeen na een scooterongeval**
  Krist GTA, <u>Jelsma J,</u> van Buul GM
  Ned Tijdschr Geneeskd. 2021;165:D5758

- **Neurology in metal-on-metal hip arthroplasty - a case of suspected PHACT**
  <u>Jelsma J,</u> Kleinveld HA, Rozemuller JM, Heyligers IC
  Acta Orthop. Belg., 2020, 86 e-supplement 1, 67-70

- **Spinal surgeons' opinions on pre- and postoperative rehabilitation in patients undergoing lumbar spinal fusion surgery: a survey-based study in the Netherlands and Sweden.**
  van Erp RM, <u>Jelsma J,</u> Huijnen IP, Lundberg M, Willems PC, Smeets RJ.
  Spine (Phila Pa 1976). 2017 Sep 6.

- **Limited benefits of the direct anterior approach in primary hip arthroplasty: a prospective single centre cohort study**
  <u>Jelsma J,</u> Pijnenburg R, Boons HW, Eggen PJ, Kleijn LL, Lacroix H, Noten HJ.
  J Orthop. 2016 Oct 26;14(1):53-58

- **B-cell lymphoma of the tibia mimicking chronic osteomyelitis – a case report and literature study**
  Eggen T, <u>Jelsma J,</u> Janssen M, Schreuder B.
  Ned. Tijd. Orthopedie. 2016 Dec;23;4;136-141

- **Monthly swelling of the knee – case report and review of the literature**
  <u>Jelsma J,</u> Mayne A, Steffanie B
  Knee. 2016 Jun;23(3):559-60

- **Simultaneous bilateral distal tibia and fibula stress fractures – case report and review of literature**
  <u>Jelsma J,</u> de Nijs R, Boons H.
  Ned. Tijd. Orthopedie. 2015 Dec;22;4:91-96

- **A painful hip after revision [Dutch]**
  <u>Jelsma J,</u> Dinjens R, Adriaensen M, Heyligers IC.
  Medisch Contact. 2014 Nov;69;46:2267

- **A blood donor with MoM hip prothesis [Dutch]**
  <u>Jelsma J,</u> Kleinveld H, Heyligers IC.
  Ned. Tijdschr. Klin. Chem. Labgeneesk. 2014 Jan;39:28-30

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Curriculum Vitae Auctoris

The author of this thesis, Jetse Jelsma, was born on the 12th of March 1989 in Leeuwarden, the Netherlands. He grew up with his parents and two older brothers. After graduation from pre-university education (VWO), OSG Piter Jelles Aldlân, Leeuwarden in 2007, he started studying medicine at Maastricht University the same year.

During his study his interest in the musculoskeletal system increased which led an internship at the Orthopaedic and Traumatology Department of Orbis Medical Centre - Sittard-Geleen, the Netherlands (dr. N.P. Kort, 2010). The foundation for this thesis and his career was laid in his final year of study at the Department of Orthopaedics and Traumatology at Atrium Medical Centre - Heerlen, the Netherlands (prof. dr. I.C. Heyligers, 2012-2013).

After his graduation as Master of Medicine in 2013 he worked briefly as a resident in Rehabilitation Medicine at Maastricht University Medical Centre, the Netherlands (prof. dr. R.J. Smeets 2013-2014). He moved away from Maastricht and continued his career as Orthopaedic resident at the Elkerliek Hospital - Helmond, the Netherlands (drs. H. Lacroix, 2014-2015).

In 2016, he moved back to Maastricht and was able to start his training in general surgery at the Zuyderland Medical Centre - Heerlen/Sittard-Geleen (dr. M. Sosef, 2016-2017). His Orthopaedic training was performed at Zuyderland Medical Centre - Heerlen/Sittard-Geleen (prof. dr. I.C. Heyligers, 2017), Maastricht University Medical Centre (dr. H.M. Staal, 2018), Máxima Medical Centre - Veldhoven (dr. R.P.A. Janssen, 2019), Zuyderland Medical Centre - Heerlen/Sittard-Geleen (dr. E.J.P. Jansen, 2020-2021) and finished with an in-depth internship with dr. R.H.M. ten Broeke and dr. J.A.P. Geurts at Maastricht University Medical Centre (2021) focussing on pelvic-, acetabular- and hip surgery. During his training he continued working on this thesis.

From the 1st of February 2022 he will start as clinical fellow in advanced hip surgery at Southmead Hospital, Bristol, United Kingdom (prof. dr. A.W. Blom). In his spare time he loves watching and participating in sports (cycling). He currently lives in the city centre of Maastricht with his beloved partner, Laura.

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