MRI Assessment for Soft Tissue Reactions in Relation to High Level of Cobalt and Chromium Metal Ions Released from Metal on Metal Hip Implants

MSc thesis

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TABLE OF CONTENTS

ABSTRACT

Objectives: This study was conducted to determine the local and systemic effects of elevated blood levels of cobalt (Co) and chromium (Cr) on adverse local tissue reactions (ALTRs), aseptic lymphocyte-dominant vasculitis-associated lesion (ALVAL), metallosis and cardiotoxicity.

Methods: We conducted two independent retrospective studies on two separate groups of patients in a single center in Quebec. To determine the local effects of elevated blood levels of Co and Cr, we retrospectively reviewed 47 patients with metal-on-metal (MoM) painful hip arthroplasties and multiple Metal Artefact Reduction Sequence Magnetic Resonance Imaging (MARS MRI) to identify the patients with positive ALTR lesions. The volume progression of pseudotumors was assessed on consecutive MARS MRI images using the Hart classification. Blood Co and Cr ions were recorded. Any indications for revisions were also noted.
Separately, to determine the systemic (cardiac) effect of the elevated Co and Cr levels we retrospectively reviewed ten patients with unilateral MoM bearing hip implant having a minimum two years follow and abnormal level of metal ions in blood. All patients were without history of any cardiac (normal electrocardiography and cardiac markers) and renal conditions. Blood metal ion and cardiac markers level were recorded for all patients. The deposition of Co and Cr ions in the heart was determined using cardiac MRI, and cardiac markers including brain natriuretic peptide (BNP) and Troponin-1 (trop-1) were determined.

Results: From all reviewed patients, we have identified 20 patients with positive ALTR lesions. The mean age of the patients and mean follow duration was 65.4 years (range: 54.7 to 85.4 years) and 8.3 months, respectively. Eight hip arthroplasties showed increased lesion size

(5 with class 2b, 2 with class 2a and 1 with class 1), ten hips had revision surgery of which six had increased levels of Co and Cr. A significant positive relationship was identified between the level of Co ions and the volume and size progression of the lesions.

For the systemic effects, a separate ten patients who had no cardiac and renal history were included in the study. The mean age of the patients was 54.90 ± 4.25 years old. Co and Cr levels ranged from 0.72 to 141.4 ug/L (mean of 43.23 ± 57.03 ug/L) and from 0.89 to 88.3 ug/L (mean of 27.78 ± 34.07 ug/L), respectively. Although a significantly positive correlation was observed between the presence of pericardial effusion and Cr levels, no other significant correlations were determined between blood metal ion levels and the cardiac parameters. Correlation for left ventricular mass was not computed since all patients had normal findings.

Conclusion: A higher Hart classification showed a tendency to increase or maintain their sizes compared to those of lower classification. Elevated of blood Co levels (but not chromium) are correlated with the volume and size progression of the lesions. Lesions type 2b and 3 have a more aggressive behaviour. Bigger lesions tend to grow, and smaller lesions can regress or can remain stable for a longer time. ALTRs associated with metal on polyethylene (MoP) are rare but are usually aggressive. On the other hand, there is no concrete evidence that elevations in the blood Co and Cr levels can cause cardiotoxicity. Thus, the absolute presence of elevated metal ions is insufficient to cause cardiac disease on the patient.

RÉSUMÉ

Objectifs : Cette étude a été menée pour déterminer les effets locaux et systémiques causés par les taux sanguins élevés de cobalt (Co) et de chrome (Cr). Un intérêt particulier sera porté sur les réactions tissulaires locales indésirables ALTR et ALVAL, la métallose et la cardiotoxicité.

Méthodes : Nous avons mené deux études rétrospectives indépendantes sur deux groupes distincts de patients dans un même centre au Québec. Pour déterminer les effets locaux des taux sanguins élevés de Co et de Cr et pour identifier les patients avec ALTR, nous avons analysé rétrospectivement 47 patients symptomatiques porteurs d'une arthroplastie de hanche métal-métal (MoM) et ayant plusieurs examens d'imagerie par résonance magnétique à séquence de réduction des artefacts métalliques (IRM MARS). Le volume et la progression des pseudotumeurs ont été évaluées à partir des images IRM MARS consécutives en utilisant la classification de Hart. Les taux sanguins de Co et Cr ont été enregistrés. Toute indication de révision a été également notée.

Séparément, pour déterminer l'effet systémique (cardiaque) causés par les taux sanguins élevés de Co et de Cr, nous avons examiné rétrospectivement dix patients porteurs d'une arthroplastie unilatérale de hanche MoM ayant un minimum de deux ans de suivi et un taux anormal d'ions métalliques dans le sang. Les patients ne présentaient pas d'antécédent cardiaques (électrocardiographie normale et marqueurs cardiaques) ni rénaux. Le taux d'ions métalliques sanguins et les marqueurs cardiaques ont été enregistrés. Le dépôt d'ions de Co et Cr dans le cœur a été déterminé par IRM cardiaque et par des marqueurs cardiaques, incluant le peptide natriurétique de type B (BNP) et la troponine-1 (trop-1).

Résultats : Parmi tous les patients examinés, nous avons identifié 20 patients avec des lésions ALTR. L'âge moyen des patients étaient de 65,4 ans (de 54,7 à 85,4 ans) et la durée de suivi

moyenne de suivi de 8,3 mois. Pour huit arthroplasties de la hanche la taille des lésions a augmenté (5 avec la classe 2b, 2 avec la classe 2a et 1 avec la classe 1) et dix hanches ont subi une chirurgie de révision. Une corrélation significative positive a été identifiée entre le taux d'ions de Co et l'augmentation du volume et de la taille des lésions.

Pour les effets systémiques, dix patients sans d'antécédents cardiaques ni rénaux ont été inclus dans l'étude. L'âge moyen des patients était de 54,90 ± 4,25 ans. Les taux de Co et de Cr variaient de 0,72 à 141,4 μg /L (moyenne de 43,23 ± 57,03 μg/L) et de 0,89 à 88,3 μg/L (moyenne de 27,78 ± 34,07 μg/L), respectivement. Seulement une corrélation significativement positive ait été observée entre l'épanchement péricardique et le taux de Cr. Aucune autre corrélation n'a pas été déterminée entre le taux sanguin d'ions métalliques et les paramètres cardiaques. La corrélation pour la masse VG n'a pas été calculée car tous les patients avaient des résultats normaux.

Conclusion : Les ALTR de class Hart plus élevée ont une tendance d'augmenter ou de maintenir leur taille par rapport à celles d'une classe inférieure. Le taux sanguin élevés de Co (mais pas de Cr) est corrélé avec l'augmentation du volume et de la taille des lésions. Les lésions de type 2b et 3 sont plus agressives. Les lésions plus grosses ont tendance à se développer et les lésions plus petites peuvent régresser ou peuvent rester stables pendant une plus longue période. Les ALTR associés au métal sur polyéthylène (MoP) sont rares mais sont généralement agressifs. D'un autre côté, il n'y a aucune preuve concrète que des élévations des taux sanguins de Co et de Cr peuvent provoquer une cardiotoxicité. Ainsi, uniquement un taux élevé des ions métalliques n'est pas suffisant pour provoquer une maladie cardiaque chez le patient.

INTRODUCTION

Through the years, total hip arthroplasty (THA) has transformed the medical world on how issues on hip problems were treated. It has become so popular when we are talking of orthopaedic intervention. In the recent decades, many THA surgeries have been performed using a variety of techniques and implants. Several researches and publications have talked about these techniques and variety of implants in an attempt to discover and describe the best one that delivers the least rate of complications as well as a long-term survival of the implant. A particular interest was directed to the elevation of cobalt (Co) and chromium (Cr) ions levels in the blood of patients who underwent THA using metal-on-metal (MoM) implants. In this context, our study aims to describe whether the occurrence of local and systemic effects in patients with the MoM implants are related to the elevation of metal ions in the blood.

CHAPTER I. REVIEW OF THE LITERATURE

1.1. The Hip Joint

The hip joint is the articulation of the pelvis (the hip bone) with the femur (the thigh bone), which connects the axial skeleton with the lower extremity. The two hip bones together with the sacrum and coccyx (posteriorly) and the symphysis pubis (anteriorly) to form the bony pelvis. (Figure 1A)

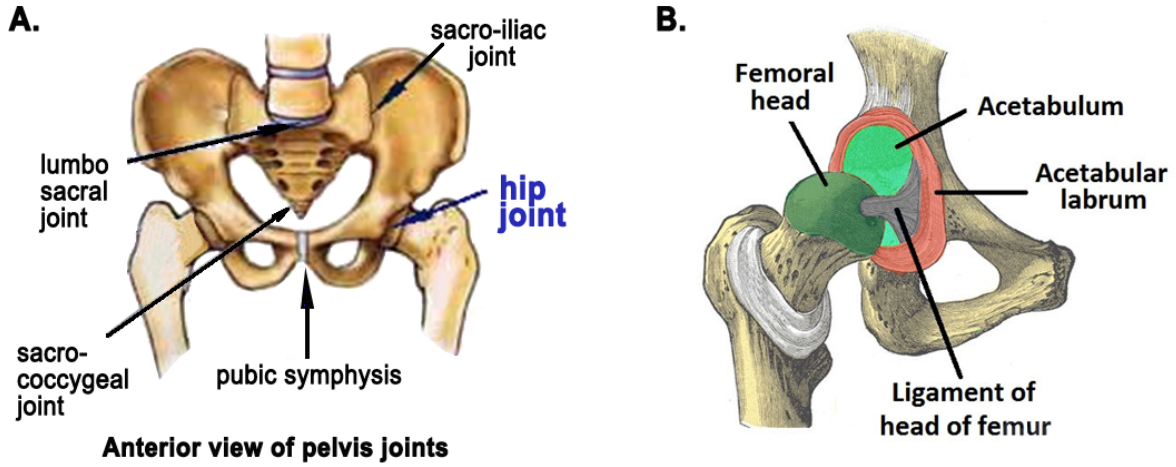

Figure 1. The hip joint: A) Anterior view of the pelvis joints. (https://courses.vcu.edu/DANC291-003) B) The components of the hip joint. The hip joint is a ball-and-socket synovial joint, composed of a "ball" which is the femoral head, and an acetabulum which forms the "socket". (https://teachmeanatomy.info/lower-limb/joints/hip-joint/)

The acetabulum is a socket that is formed by the articulation of the ilium, the pubis, and the ischium. It is located on the lateral aspect of the pelvis forming a bowl shape where the head of the femur articulates. The femoral head is the superior end of the femur (which has a smooth, spherical surface that articulates with the acetabulum. It is covered with articular cartilage except at a small area (the fovea) where the ligamentum teres (ligament of the head

of the femur) is attached that is connecting the femoral head to the acetabular notch of the hip bone. (Figure 1B)

1.2 Hip Arthroplasty

Hip reconstruction or hip arthroplasty (HA) was introduced in the late 60's and remains one of the most widely performed procedures in orthopedics proven to successfully relieves pain and restores function to patients whose joints have been destroyed by trauma or disease. Although the main cause for HA (90% of cases) is osteoarthritis (OA) (Blom et al, 2008), other medical conditions have been successfully treated by hip replacement. It is also indicated and performed among patients who have rheumatoid arthritis, post-traumatic arthritis, fractures of the hip, and avascular necrosis. HA is also used as primary treatment and allow patients to mobilize after intertrochanteric fractures of the hip (Sidhu et al, 2010), femoral neck fractures (Sobie, 2003), acetabular fractures secondary to trauma (De Bellis et al, 2014; Ranawat et al, 2009; Jimenez et al, 1997), and displaced femoral neck fractures (Chammout et al, 2012). It is also performed on patients with coxarthrosis secondary to congenital dysplasia and dislocation of the hip (MacKenzie et al, 1996). Patients with avascular necrosis in systemic lupus erythematosus and sickle cell disease are also managed by HA with good clinical outcomes (Bose et al, 2010; Schneider et al, 2004; Mousawi et al, 2002; Zangger et al, 2000). Among renal transplant patients, osteonecrosis of the femoral head is a common complication, and HA was found to be a safe and effective treatment (Radford et al, 1989).

Between 1990 to 2002, the National Hospital Discharge Survey (NHDS) data indicates a 50% increase in total number of HA procedures in the United States (Kurtz et al, 2005). In March 2014, the Mayo Clinic Orthopedics Study reported that over 2.5 million Americans have undergone THA. By 2030 the demand for HA was projected to grow by 174% (Kurtz et al, 2007).

HA is recommended for patients with limited daily activities because of continuous pain that is not relieved by anti-inflammatory drugs, physical therapy or walking supports. Patients are carefully evaluated including medical history, physical and radiologic examinations and other tests including magnetic resonance imaging (MRI).

HA consist of the replacement of the damaged bone and cartilage of the hip by prosthetic materials. The femoral head (Figure 2) is detached out of the acetabulum (the socket) and the latest is repaired by removing the damaged bone and cartilage. An artificial cup is placed either cemented or by "press fit". Then a liner is fitted into the cup, which now forms the new socket called the "acetabular component". The "femoral component" of the hip joint is done by removing the head of the femur and is replaced by an artificial head that is fitted accordingly to the acetabular component. The femoral component will then be plugged into the acetabular component to form the hip joint (Figure 2).

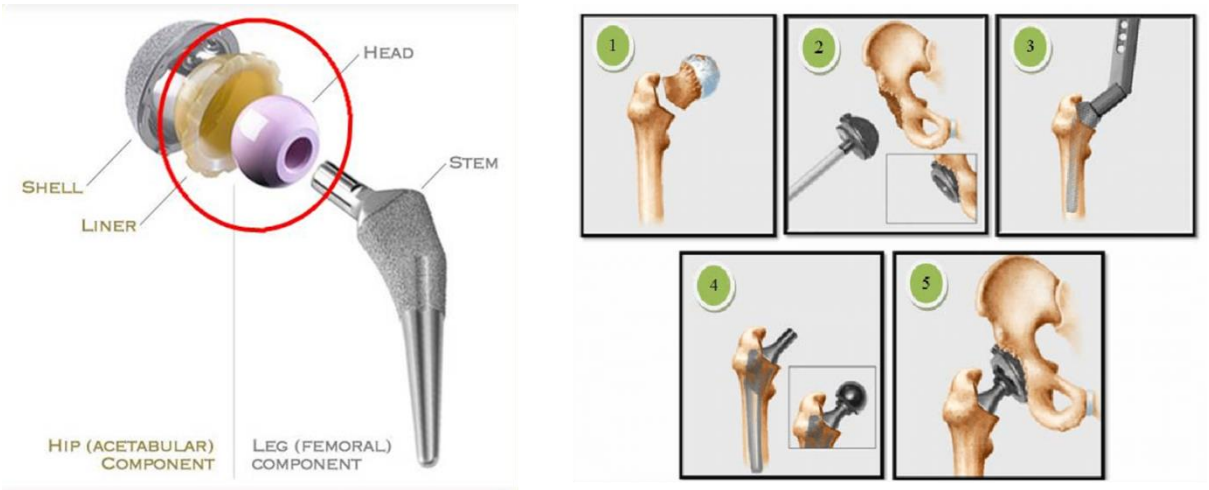

Figure 2. Total hip arthroplasty and bearing surfaces. Illustrating the elements of hip implant with its bearing surface. (https://www.slideshare.net/drashwanipanchal/total-hip-replacement-discussion)

1.3. Bearings Surfaces

Compared to healthy, organic cartilage surfaces, which have a surface friction of nearly zero, the friction between implant bearing surfaces is hundreds of times higher. This friction subjects the implant components to wear that can limit the longevity of the joint replacement and induce inflammatory responses in the tissues surrounding the joint itself. The problem of wear in hip replacement implants has led to the reintroduction of many alternative bearing combinations with low friction.

Metal on Metal (MoM): The ball and the socket replacement components of the hip joint are made of metal. Most hip replacements nowadays are manufactured using cobalt and chromium alloys, or titanium. (Figure 3).

Polyethylene and Metal on Polyethylene (MoP): Introduced by Sir John Charnley in the early 1960's, this type of implant uses ultrahigh molecular weight polyethylene cup with a metallic femoral head. Although it has been frequently used for several decades, it was known that this produces osteolysis secondary to particle debris on both acetabular and femoral sides (Garcia-Cimbrelo & Munuera, 1992; Hallan et al, 2006; Oroshimo et al, 2003; Cruz-Pardos et al, 2001; Maloney et al, 1999).

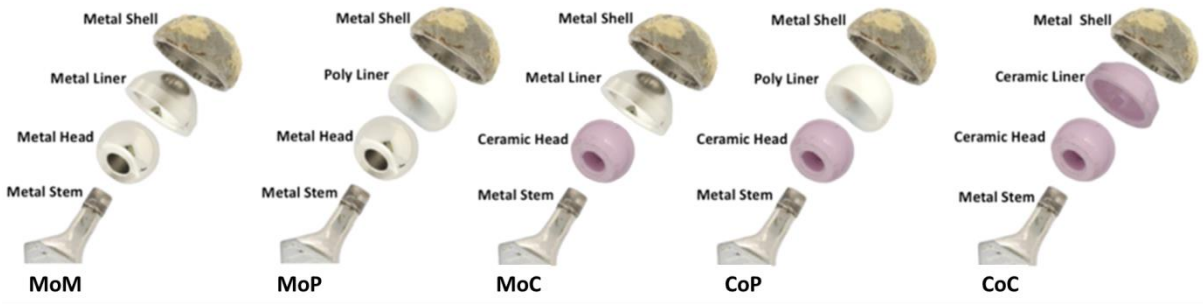

Figure 3. The most commonly used bearing surfaces. (http://www.lirc.co.uk/hips)

Ceramic on Metal (CoM): The CoM is designed with a ceramic head and a metal acetabular component. This type of implant has been shown to decrease the wear and friction compared

to other types of implant because of its smoother surface and hardness (Williams et al, 2007; Figueiredo et al, 2008).

Ceramic on Ceramic (CoC): The CoC uses a ball and socket which are made of ceramic material. They are designed to resist wear and tear since they are scratch-resistant, and smoother compared to other implant materials. However, studies have shown that this type of implant had problems including breakage and squeaking (Ha et al, 2007; Jarrett et al, 2009).

Ceramic on Polyethylene (CoP): The use of CoP has increased from 11.1% in 2007 to 50.8% cases in 2014 (Heckmann et al, 2018). Studies have shown that CoP has the lowest reported rates of fracture and audible component rates compared to the COC implants (Amanatullah et al, 2011).

1.4. Focus on Metal on Metal (MoM) hip implants

1.4.1. History of MoM hip implants

According to the literatures the first use of a MoM bearing is attributed to P. Wiles, who performed THA on a patient using an implant made of steel (Wiles, 1958). The first-generation of state-of-the-art MoM bearings was developed by G McKee and J Watson-Farrar in the 1960s. However, its use was associated with increased rate of failure due to poor metallurgy, poor manufacturing techniques and inferior implant designs. The casting process used to make metallic implants suffered from poor quality control. This sometimes resulted in products that had inferior wear resistance, and which were prone to fracture in the body.

However, improved metallurgy and manufacturing techniques led to resurgence in the use of MoM bearings for hip replacement Thus, in the mid-1970's MoM bearings regained popularity (Brown et al, 2002) and in 1988, Weber introduced a second-generation of implants with MoM bearings (Triclot, 2011).

1.4.2. Increase in the use of MoM hip implants, advantages and disadvantages

The most widely used MoM bearings were made of cobalt-chromium alloys. These bearings were popularized due to their low volumetric wear rate compared to MoP bearings (Shimmin et al, 2008), greater longevity, increased stability and greater range-of-motion with larger diameter bearings when properly placed (Schmalzried, 2009; Van Sikes et al, 2008). The use of larger MoM femoral heads provides also the restoration of normal motion and gait patterns (Quesada et al, 2008), increasing the functional levels (Newman et al, 2008). Therefore, improved manufacturing technology and a better understanding of the factors influencing MoM component wear made this new generation of bearings promising (Kim et al, 2008; Long, 2005; Tardy et al, 2015), especially for young and active patients (Shetty et al, 2011; Delaunay et al, 2008); Girard et al, 2010).

The problems with MoM bearings began to appear in 2005 when the national joint registries have reported the failure rate of THA with MoM bearings to be 2–3 fold higher than contemporary THA with non-MoM bearings (Dahlstrand et al, 2017), associated with local bone and soft tissue necrosis, with pseudotumor formation comprising a predominantly lymphocytic inflammatory reaction and, wear particles in the form of Co and Cr ions have been detected throughout the body (Pandit et al, 2008; Kwon et al, 2011; Campbell et al, 2010; Williams et al, 2011).

1.4.3. Safety alert from both FDA and MHRA.

Numerous studies have reported local hip symptoms and elevated levels of metal have been found in serum and urine from patients with MoM hip replacements (Tower, 2010; Jantzen et al, 2013; Bradberry et al, 2014; Brodner et al, 2000; Ohtsuru et al, 2017). These metal ions and particle debris can enter the bloodstream, transported to distant locations in the body and

deposited in vital organs as the heart, thyroid, and kidneys (Tower, 2010; Bradberry et al, 2014; Brodner et al, 2000). Although high concentration of Co and Cr are needed to produce a health problem, systemic toxicity at lower doses have also been reported to cause adverse reactions and malfunctioning of MoM bearings (Leyssens et al, 2017). A report suggested that osteoclasts were more sensitive to metal ions exposure and may affect the bone health of patients leading to bone-related complications brought about by these implants (Andrews et al, 2011).

For this reason, in February 2011, the Food and Drug Administration (FDA) issued a public safety communication on the use of MoM bearings. In January 2013, the FDA proposed the requirements for all MoM implants and published the final order in May 2016 for all manufacturers to stop marketing their MoM implants without FDA approval date. Since 2016, there are no FDA-approved MoM HA replacement devices in the FDA of the United States. (Figure 4)

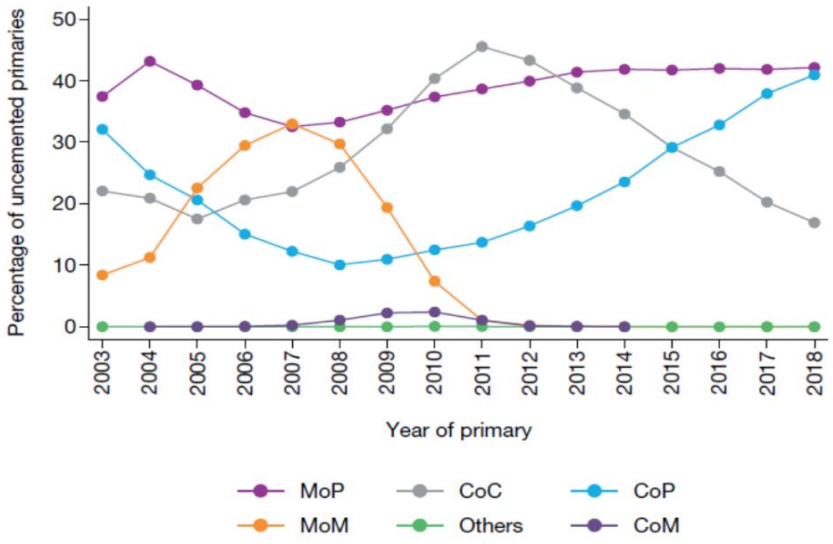

Figure 4. Safety alert on metal ions accumulation (2003-2018). (United Kingdom National Joint Registry, 2018)

The United Kingdom Medicines and Healthcare products Regulatory Agency (UK-MHRA) issued an alert on June 29, 2017 to early detect soft tissue reactions in patients implanted with MoM hip replacements (UK-MHRA, 2017). Health regulators and various health agencies worldwide has issued the desire to totally ban and phase-out the use of MoM because of high failure rates and the mutagenic effect of Co and Cr particles on the surrounding tissues (British Orthopaedic Association, 2012).

1.5. Cobalt and Chromium metal ions

Cobalt (Co^{27}) is an essential dietary trace element found in nature as arsenides, oxides, and sulphides and the forming component of the vitamin B12 (hydroxycobalamin) (Barceloux & Barceloux, 1999). Chromium (Cr^{24}) is considered an essential nutrient in humans for insulin and insulin resistance, sugar and lipid metabolism (Havel, 2004; Davis et al, 1997). Co^{27} ions are more soluble than Cr^{24} ions, but Cr^{24} binds more readily to proteins than Co^{27}, thus they accumulate more in soft tissues than Co^{27} (Fehring et al, 2015).

The levels of metal ions released are dependent on the type of MoM implants and can raise in the blood from 0.7 to 217 ug/L (Lavigne et al, 2011; Malviya et al, 2011; Garbuz et al, 2010). These concentrations remain elevated after surgery, but complication rates may vary between patient to patient and duration of implant (Qu et al, 2011).

Several factors can influence metal levels in such cases, including the diameter of the joint. As the size of the femoral head of the joint increases, so does the amount of wear. For example, resurfacing of the hip is employing a large metallic cap secured to the head of the femur and a matching large metallic shell in the acetabulum. Indeed, MoM resurfacing patients have a significantly greater increase in serum Co and Cr levels than patients with a conventional total hip with a much smaller diameter MoM bearing. The highest metal ion concentrations were reported after treatment with stemmed large-head MoM-implants and hip resurfacing

arthroplasty (Hartmann et al, 2013). A cup inclination (steep inclination) greater than 50 degrees was also found to be associated with an increase in the serum Co and Cr from 1.66 ppb and 1.88 ppb to 4.45 ppb and 4.3 ppb, respectively (Hart et al, 2008; De Haan et al, 2008). Implant design such as the Corail-Pinnacle implants were found to produce lower blood metal ions compared to other implant designs (Matharu et al, 2015).

Despite the increases of metal ion concentration, studies have shown that these levels may decrease over time, much more among female patients (Savarino et al, 2014).

1.6. Local effects of metal ions

1.6.1. Adverse local tissue reactions (ALTRs)

ALTRs are local responses and/or damage of tissues surrounding the implant and joint and have been often reported among MoM patients (Engh et al, 2010). The prevalence of ALTRs vary widely in the literature from 0.1 – 71% (Fehring et al, 2014; Wiley et al, 2013) and 31% incidence of ALTRs was found among asymptomatic patients with MoM hip implants (Fehring et al, 2014).

Corrosion at the head-neck taper is thought to initiate a cascade of events leading to ALTRs and it was found to be associated more with MoM than MoP bearings (Fricka et al, 2012; Jacobs et al, 2014). Additionally, corrosions were mostly found at the articulating surfaces among patients with large-diameter MoM bearings (Whitehouse et al, 2013) and were found to be the potential cause for new-onset pain (Cooper et al, 2013). Concomitant infection with or without ALTRs are also usually found among patients with MoM bearings (Judd & Noiseux, 2011). Studies have shown that patients who develop ALTRs to MoM bearing surface have a higher possibility of reoperation (Engh & Ho, 2010) and up to 14.3% of patients who develop ALTRs must undergo revision surgery (Wiley et al, 2013). However, ALTRs following THA still remains controversial.

1.6.2. Aseptic lymphocyte dominated vasculitis associated lesions (ALVAL)

ALVAL occurs as a delayed hypersensitivity reaction that describes joint effusion in the absence of infection. The prevalence of ALVAL were reported to be around 13% as systemic hypersensitivity Type IV reactions measured by lymphocyte proliferation (Known et al, 2010). The occurrence of ALVAL has become a significant clinical problem among patients with MoM hip bearings, since it results to implant failure (Duggan et al, 2013; Hutt et al, 2011). A persistent groin pain may indicate the presence of ALVAL, and despite the type of hip implant, patients' activity levels decrease, and pain increase 6 months to a year following the procedure (Jameson et al, 2010).

1.6.3. Metallosis

Metallosis develops as metal ions build up in the tissue around the MoM hip implants and is described as macroscopic necrosis due to metal debris in soft tissues causing periprosthetic osteolysis, aseptic loosening (Korovessis et al, 2006) and cystic lesions in the groin (Gruber et al, 2007). Metallosis may also occur when there is an impingement between the socket and the femoral neck of the MoM bearing (Iida et al, 1999). Reports have shown that metallosis causes various symptoms including sensory disturbance, hearing loss, and hypothyroidism (Ikeda et al, 2010). However, several studies have shown a decrease of metal ion levels after removal of the MoM hip implants in patients with symptomatic metallosis (Ebreo et al, 2011; Vendittoli et al, 2011).

1.6.4. Pseudotumor formation

Pseudotumors are cystic or solid non-infective or malignant condition around the MoM hip prosthesis (Bosker et al, 2012; Matthies et al, 2012; Beaule, 2011; Malviya & Holland,

2009; Drummond et al, 2015; Kwon e al, 2011; Williams et al, 2011; Hart et al, 2012; Pandit et al, 2008; Campbell et al, 2010). They were found present in up to 55% of patients with significantly elevated Co and Cr levels (Kwon et al, 2011; Williams et al, 2011; Hart et al, 2012). Other authors suggested that approximately 1% of patients who have MoM with an ASR device develop pseudotumors within five years (Pandit et al, 2008).

Histological examination of these pseudotumors revealed necrosis of the connective tissues within the pseudotumor with cystic degeneration, with more macrophages and metal particles (Pandit et al, 2008; Campbell et al, 2010). It was suggested that corrosion at the neck-stem tapers causes the release of metal ions to the surrounding structures and causing pseudotumor formation (Gill et al, 2012). However, there were also studies that suggested that a well-positioned large diameter MoM bearing has a lower incidence of pseudotumor formation (Ando et al, 2018). Although pseudotumor formation was also reported with other types of bearings such as MoP, the most reported cases remain with the MoM (Walsh et al, 2012).

1.7. Systemic effects of metal ions

At high concentrations, Co toxicity (cobaltism) is reported to induce cellular apoptosis and necrosis with inflammatory response (Cheung et al, 2016). It was thought to cause oxidative DNA damage combined with inhibition of DNA repair (Simonsen et al, 2016). A recent study reviewed the 18 published cases where Co toxicity has been attributed to the use of Co-Cr alloys in hip arthroplasty (Zywiel et al, 2016). The study revealed that majority of these cases reported systemic toxic reactions at serum cobalt levels more than 100 μg/L

1.7.1. Neurologic effects

Neurologic symptoms are very common among hip arthroplasty patients with metal ion toxicity (Devlin et al, 2013). Severe Co toxicity was reported up to four years after the

implantation in seven patients who had McKee HA. These patients presented with progressive pain, feeling of instability and two patients had spontaneous dislocation of the hip (Jones et al, 1975). Neurological manifestations including hand tremors, diminished coordination, slow cognition, poor memory and lassitude developed in a patient 30 months after THA with MoM implant (Tower, 2010). In another study, patients with MoM hip implants and markedly elevated levels of serum metal ions sought evaluation for fatigue, tinnitus and hearing loss. These patients were minimally symptomatic and seek guidance regarding elevated metal ions, which subsequently decreased after the revision of their hip implant (Leiken et al, 2013). Other neurologic features related to THA using MoM include ocular toxicity presenting as visual impairment, and peripheral neuropathy that is more associated with metal toxicity (Bradberry et al, 2014; Mann et al, 2012; Ikeda et al, 2010; Sotos et al, 2013).

1.7.2. Effects on the thyroid

Apart from the neurologic manifestations, reports of metal toxicity have shown to cause thyroid dysfunction in many cases. Thyroid dysfunction can either manifest as hypothyroidism or hyperthyroidism (Tower, 2012; Brent & Devlin, 2013; Tvermoes et al, 2015). Researchers suggested that metal ions particularly Co inhibits tyrosine iodinase that results in thyroid hyperplasia and hypothyroidism (Prentice et al, 2013). Signs and symptoms of thyroid dysfunction (and other systemic effects) were reported to appear 3 to 72 months after arthroplasty which include neck discomfort, fatigue, weight gain or feeling cold (Devlin et al, 2013).

1.7.3. Effects on the kidneys, kidney absorption and excretion of cobalt and chromium

It is well known that kidneys are the first target organ in cases of heavy metal toxicity. Cr and Co are non-essential and non-biodegradable elements that can be toxic at very low doses to the kidneys, depending of route and duration of exposure (Barbier et al, 2005). It has been

suggested that the main channel of excretion of water-soluble Co is through the gastrointestinal system and absorbed from the small intestine to the blood. However, once Co level increased in the blood, it indicates that the elimination process of Co has become low, and that the kidney is the primary organ that is responsible for the elimination (Kent and McCance, 1941). It was reported that renal excretion of Co is initially rapid. However, this excretion slowly decreases over several weeks followed by tissue retention for several years (Simonsen et al, 2016). On the other hand, Cr is thought to be absorbed from the gastrointestinal tract by passive diffusion, transported to the bloodstream by iron transport protein transferrin and then eliminated by the kidneys through the low molecular-weight chromium binding substance (LMWCr) (Vincent & Edwards, 2019).

Co and Cr concentrations particularly in patients who are on maintenance hemodialysis were found to remain high despite dialysis which were found to be not effectively working on these chelating agents because of its being protein bound (Curtis et al, 1976). High levels of Cr in a patient who underwent four hours of hemodialysis was found to be ineffective and neither affect the progression or outcome of his intoxication because of its being protein bound (Iserson et al, 1983). It was also suggested that long-term exposure to Cr causing acute tubular necrosis (ATN) may produce a persistent renal injury because of its ability to form polymeric chains and is affected by lactate which is a common substance in dialysate that plays an important role in the mobility and subsequent transfer of Cr ions across the peritoneum (Wallaeys et al, 1988).

1.7.4. Effects on the heart

Cobalt cardiomyopathy was first described in 1967 in patients with excess dietary cobalt, ‘Quebec beer-drinkers’ cardiomyopathy’. Concerns have been recently raised about heart pathology and MoM implants composed of cobalt-chromium alloy (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015). Reports have shown that Co

toxicity could lead to heart failure and cardiomyopathy (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015). Suggested theories include Co interference with the cardiac myocyte oxygen uptake and transmembrane transport system disruption (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015). Other studies advocate that Co toxicity was due to oxidative stress causing direct cellular toxicity (Cheung et al, 2016). Histopathological findings in Co related cardiac toxicity include myofibrillar hypertrophy, interstitial fibrosis and muscle fiber degeneration (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015).

Most case reports of cardiac toxicity in patients with MoM bearings were mainly associated with extremely elevated blood Co levels of > 100 pbb (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015). In each case, the authors have noted significant malpositioning and/or degradation of the metal component(s) of the device. Additionally, it was suggested that the MoM articular surface replacement (ASR) XL acetabular system is significantly associated with higher rate of hospitalization for heart failure, and with other types of implants (Gillam et al, 2017).

The first documented case of MoM THA Co cardiac toxicity was reported in a 69-year old female who presented with heart failure after having MoM THA. Her Co and Cr levels in blood were 199 pbb and 77 pbb, respectively. She died of cerebral infarction on the 7^{th} post-operative day after revision (Martin et al, 2015). A diastolic dysfunction was found by echocardiography in a patient at 43 months after arthroplasty (Tower, 2010) while Moniz et al. reported a case of cardiac transplantation as a direct result of Co and Cr toxicity after a MoM hip replacement surgery (Moniz et al, 2017).

Despite all these reports, other controversial studies have shown that even in the presence of raised serum and blood Co and Cr levels of patients who had MoM THA (18-153 ug/L), no cardiac effects may be identified (van Lingen et al, 2013). A more recent study showed that

high blood Co and Cr levels have no significant cardiotoxic effects on patients with MoM hip implant verified by echocardiography, cardiac MRI and cardiac blood biomarkers (Berber et al, 2017). Additionally, patients who have undergone MoM THA with a well-functioning implant even those with pre-existing risk factors were found to have lower risks to develop cardiac effects (Gillam et al, 2017).

1.8. Metal Artifact Reduction Sequence (MARS) MRI technology

Metal artifact reduction sequence (MARS) refers to a specific pulse sequence used in reference to concepts and techniques of metal suppression (Olsen et al, 2000). It reduces the size and intensity of susceptibility artifacts from a magnetic field distortion (Olsen et al, 2000). This technology was shown to quantify and blur metal noise which results in least image distortion, reducing the artefact by an average of 79% (Kolind et al, 2004). It improves detection of avascular necrosis and allows improved visualization of the issues adjacent to the implanted material (Olsen et al, 2000).

Studies have shown that the MARS sequence effectively reduces the degree of tissue obscuring artifacts and improves the image quality compared to the conventional T1-weighted spin-echo sequence (Chang et al, 2001). A prospective cohort study that compared the diagnostic accuracy of MARS MRI to ultrasound scanning showed a higher sensitivity of MARS MRI in the detection of pseudotumors and muscle atrophy in patients with painful MoM hip arthroplasty (Siddiqui et al, 2014).

The Hip Society suggested an algorithm approach to management of hip arthroplasty patients returning for follow-up (symptomatic or asymptomatic) MoM articulation, and this includes MARS MRI (Figure 5, Figure 6) (Lombardi et al, 2012).

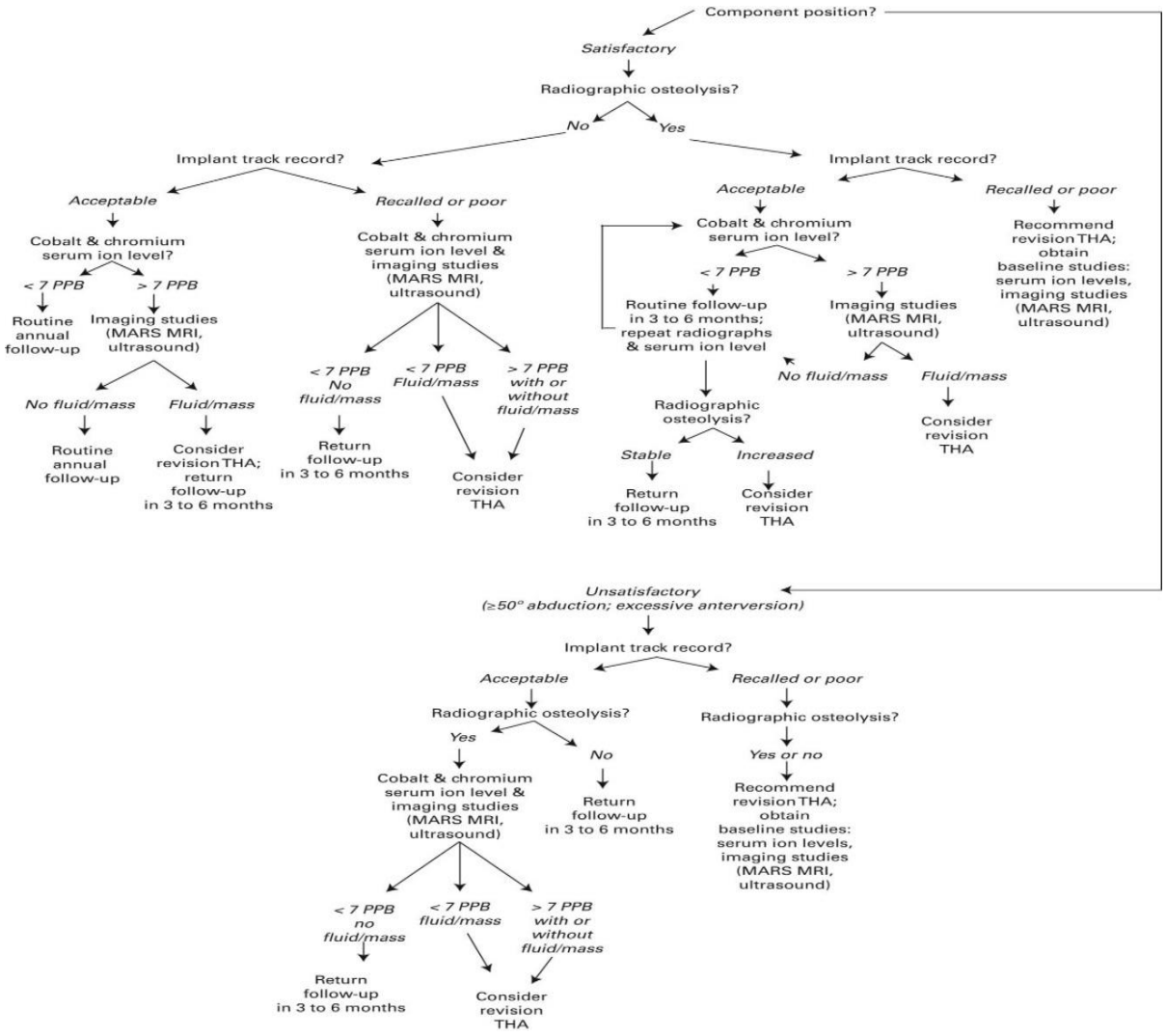

Figure 5. An algorithm outlining the steps recommended for evaluating a patient who presents in follow-up after hip arthroplasty with an asymptomatic MoM bearing (Lombardi et al, 2012).

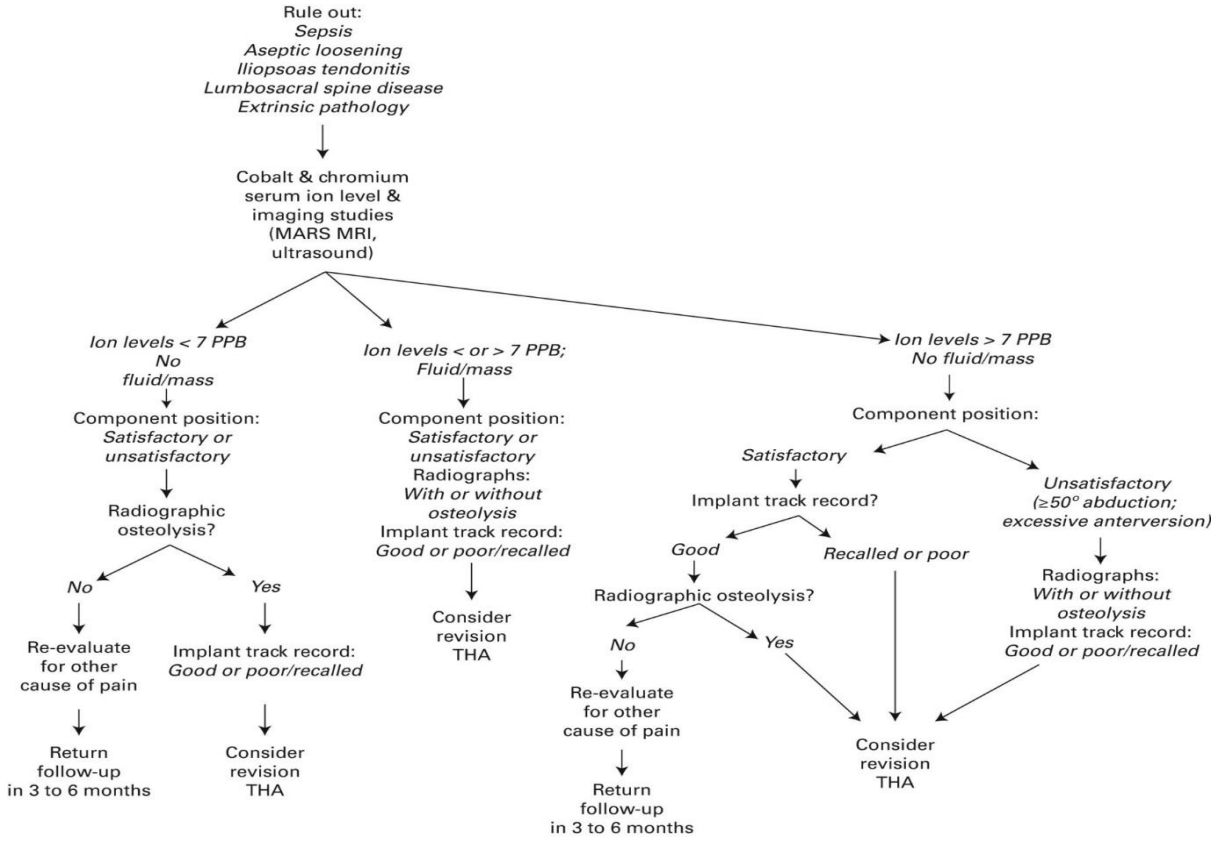

Figure 6. An algorithm outlining the steps recommended for evaluating a patient who presents in follow-up after hip arthroplasty with a symptomatic MoM bearing (Lombardi et al, 2012).

1.9. Functional Cardiac MRI.

Functional cardiac MRI has become more increasingly popular in the assessment of myocardial viability and perfusion. The Health Quality Ontario published a detailed evidence-based analysis on the effectiveness and safety of functional cardiac MRI (Health Quality Ontario, 2003). In their report, they highlighted the more superior performance of functional cardiac MRI for the assessment of myocardial viability and perfusion compared with other imaging techniques in the diagnosis of coronary artery disease. However, they also pointed out some limitations in the performance of functional cardiac MRI when it comes to small sample size, in patients who had undergone revascularization, patients with prior MRI, in patients with left ventricular ejection fraction of >35% and poor interobserver agreement (Health Quality Ontario, 2003). There has been also a lack of studies on the economic and cost-effectiveness of functional cardiac MRI compared to other diagnostic imaging techniques.

A study showed that functional cardiac MRI was able to demonstrate subtle changes in the structure and function of the heart that correlates with systemic metal ion measurements as a consequence of wear debris among patients with MoM hip resurfacings (Juneau et al, 2019). Another study followed up 35 patients with a mean of 8 years after MoM resurfacing surgery and evaluated the cardiac function using functional cardiac MRI, which showed 7% lower cardiac ejection fraction and a 6% larger left ventricular end-diastolic diameter compared to patients who had conventional hip replacement surgery (Prentice et al, 2013).

One of the first cases of cardiomyopathy resulting from systemic cobalt toxicity after MoM THA was shown in a functional cardiac MRI in a 54-year-old man who presented 5 years after hip replacement surgery with a Biomet M2a-Magnum MoM prosthesis. He presented with chest pressure with exertion, fatigue and diaphoresis. Echocardiogram showed mitral regurgitation, stage II diastolic dysfunction with left ventricular ejection fraction of 55% with no suggested cardiac ischemia. His Co level was elevated at 120 pbb and Cr level was 109 pbb.

Functional cardiac MRI was performed and defined a fulminant myocarditis of toxic origin, and diagnosis of cardiac amyloidosis was excluded. Biopsy then revealed cobalt cardiomyopathy (Mosier et al, 2016).

The future of performing a functional cardiac MRI particularly among asymptomatic patients who have undergone MoM hip replacement surgery or among patients who have a well-functioning MoM implants need to be further elucidated. For now, the capability of functional cardiac MRI to demonstrate subtle changes in the structure and the function of the heart is consistent with systemic elevations of the metal ions (Juneau et al, 2019).

1.10. Research Problem

ALTRs are local responses and/or damage of tissues surrounding the implant and joint. Several studies have reported ALTRs among MoM patients. The prevalence of ALTRs vary widely in the literature from 0.1 – 71% (Fehring et al, 2014; Wiley et al, 2013). A 31% incidence of ALTRs was found among asymptomatic patients with MoM hip implants (Fehring et al, 2014). The corrosion of the femoral head taper was found to be associated more with MoM compared to MoP implants and was found to worsen with time (Fricka et al, 2012; Jacobs et al, 2014). Corrosions were mostly found at the articulating surfaces among patients with large-diameter MoM hip arthroplasties with persistent symptoms (Whitehouse et al, 2013), and were also found to be the potential cause for new-onset pain inpatients with MoM implants (Cooper et al, 2013). Concomitant infection with or without ALTRs are also usually found among patients with MoM hip implants (Judd & Noiseux, 2011). Studies have shown that patients who develop ALTRs to MoM bearing surface have a higher possibility of reoperation (Engh & Ho, 2010). Up to 14.3% of patients who develop ALTRs have to undergo revision surgery (Wiley et al, 2013). ALTRs following THA remains controversial. Also, the high prevalence of reported ALVAL among patients who have undergone hip arthroplasty with

MoM implants continue to raise concern among patients and surgeons as well (Duggan et al, 2013; Hutt et al, 2011). The accumulation of high levels of metal ions from MoM implants causing metallosis and pseudotumor formation, and eventually failure of the implant and the need for revision (Korovessis et al, 2006; Gruber et al, 2007; Ebreo et al, 2011; Vendittoli et al, 2011; Bosker et al, 2012; Matthies et al, 2012; Beaule, 2011; Malviya & Holland, 2009; Drummond et al, 2015; Kwon e al, 2011; Williams et al, 2011; Hart et al, 2012; Pandit et al, 2008; Campbell et al, 2010).

The HA with MoM bearing of CoCr alloys may release Co and Cr particles (ions) in the systemic circulation due to mechanical wear or corrosion mechanisms. Furthermore, the released metal ions can deposit in vital organs like the heart (Ong et al, 2009; Blom et al, 2003). Cardiotoxicity is considered as possible adverse reaction to metal ions wear debris from such implants and could lead to several complications, like heart failure and cardiomyopathy. However, the direct impact of these metal ions on the occurrence of cardiac disease is still not fully appraised and less clear. In addition, causal associations between MoM bearing hip implants and the potential risks have not yet been established; nor have safe levels for metal ions. (Blom et al, 2003; Urquhart et al,2010). Nevertheless, cardiotoxicity due to systemic Co or Cr level elevations have been more recognized lately. In addition, heart failure is common in the patient population most likely to undergo hip replacement, so there is concern that an association between MoM hip implant and heart failure (Bongartz et a, 2008; Phillips et al, 2003).

HYPOTHESES

1. Local effect

Elevated blood Co and Cr ion levels have a strong correlation with size of the local lesion

2. Systemic effect

Elevated blood Co and Cr ion levels have a significant cardiotoxic effect

Objectives based on the hypotheses

Local

- Determine the relationship between metal ion levels and size or progression of the lesion.
- Determine the safety and the need to revise MoM bearings implant.
- Determine the best time for intervention before the development of further irreversible tissue damage.

Systemic

- Determine the potential of a comprehensive panel to establish markers of early cardiotoxicity.
- Assess the effect of elevated whole-blood metal ion levels on cardiac function
- Determine the safety and the need to revise MoM bearings implant.

CHAPTER II. METHODOLOGY

2.1. Local effects

We conducted a retrospective review of all patients with painful hip arthroplasties and positive for ALTR lesions having multiple MARS MRIs seen and managed between January 2000 and December 2018. Data on the MARS MRI evaluation and blood metal ion analysis of patients admitted during the time frame mentioned above were extracted and analyzed. Cases with positive ALTR on sequential MRI and the indications for revisions were also noted. The volume progression of pseudotumors was identified using the Hart classification that defined as Type 1 if pseudotumor is cystic with internal fluid echo-texture, flat, and thin-walled; Type 2 if pseudotumor internal fluid echo-texture, atypical fluid, and irregular thick-walled; and Type 3 if pseudotumor is solid with complex solid echo-texture (Hart et al, 2012). Serum cobalt and chromium ions were recorded.

Statistical analysis using the Statistical Package for Social Sciences (SPSS) volume 23.0 (SPSS Inc, IBM, Armonk, New York, USA) was used to analyze the data. Results were reported as numbers and percentages. Pearson correlation was used to determine the significant relationship between the levels of cobalt and chromium ions with the volume and size progression of the lesions, and between volume progression using the Hart classification and size and volume of the lesions. A p value of ≤ 0.05 was considered statistically significant.

2.2. Systemic effects

We included ten patients from a single center to determine the systemic effects of blood metal ion levels (cobalt and chromium). All patients included have primary unilateral MoM bearing hip implant, with at least two years follow up after the surgery, and abnormal blood

metal ions levels. All patients were without any cardiac history (normal ECG and cardiac markers) and history of renal conditions.

We assessed the blood metal ions and the cardiac markers level in the blood in all patients. The deposition of Co and Cr ions in the heart was determined using cardiac MRI. Cardiac function was evaluated using the cardiac markers including BNP and trop-1 corelated with metal ions level in the blood. Other data collection included BMI, age at surgery, gender, other medical comorbidities (diabetes, previous heart conditions, smoking, COPD, dyspnea, hypertension, etc.).

Results were expressed as number and percentages for categorical variables and as mean and standard deviation for continuous variables. The correlations between metal ions levels in the blood and ejection fraction values were calculated using the Pearson correlation coefficient. A multivariate regression was used to determine the effect of metal ions in blood on cardiotoxicity. Statistical Package for Social Sciences (SPSS) version 23.0 (IBM, SPSS, Armonk, New York, USA) was used in the analysis of the collected data. A p value of ≤ 0.05 was considered statistically significant.

CHAPTER III. RESULTS

3.1 Local effects

3.1.1. General demographic characteristics of the patients

Table 1 shows the demographic characteristics of all patients. A total of 20 patients were included in the study, 12 (60.0%) had resurfacing hip arthroplasty (RHA), 4 (20.0%) had MoM hip arthroplasty, 3 (15.0%) had MoP hip arthroplasty, and 1 (5.0%) had CoM hip arthroplasty. The mean age for all patients was 65.4 years (range: 54.7 to 85.4 years), and the mean duration of follow up was 8.3 months. Half of the patients (50.0%) had revision surgery.

Table 1. Demographic characteristics of the 20 patients with ALTR lesions on sequential MARS MRI.

Demographics	All cases	RHA	MoM	MoP	CoM	Statistical analysis
Number of patients	20	12	4	3	1	
Number of hips	23	15	4	3	1	
Mean age in years (range)	65.4 (54.7 – 85.4)	61.4 (54.7 – 73.4)	61.8 (56.4 – 66.5)	83.7 (81.5 – 85.3)	59.7	Patients who underwent MoP were statistically older compared to RHA, MoM and CoM ($p<0.001$)
Follow up in years	8.3	7.8	8.2	11.9	4.7	There was no statistical difference in the length of follow-up between RHA, MoM, MoP and CoM ($p>0.05$)
Time between 1st and last MRI, in months	2.2	2.2	1.6	2.3	4.2	No statistical difference in the time elapsed between 1st and last MRI $p>0.05$
Number of revised cases	10 (43%)	7 (46.6%)	1 (25%)	2 (66.7%)		

Note: RHA-resurfacing hip arthroplasty; MoM-metal on metal hip arthroplasty; CoM-ceramic on metal arthroplasty; MoP-metal on polyethylene arthroplasty.

3.1.2. Blood Co and Cr ion levels and its correlation with the size of the local lesion

Figure 7 shows the volume progression with Hart classification. Eight hip arthroplasties showed with increased size (5 with class 2b, 2 with class 2a and 1 with class 1). Pseudotumors of higher Hart classification showed a tendency to increase or maintain their sizes compared to those of lower classification.

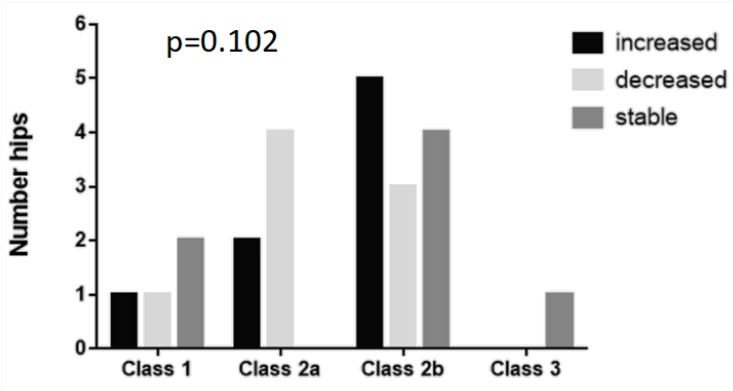

Figure 7. Volume progression with Hart classification (Class 1 and 2a=fluid-filled MRI findings, 2b=mixed type, Class 3=solid finding).

3.1.3. Blood Co and Cr ion levels and its correlation with the progression of the local lesion

There was a significant positive relationship that was identified between the level of cobalt ions with the volume (p=0.0011) and size progression of the lesions (p=0.0268). However, no significant relationship was established between Co ions level and the type of the lesion (p=0.8527). Figure 8 shows the relationship between the level of cobalt with the volume and size of progression of the lesions while Figure 9 shows the relationship between the level of chromium with the volume and size of progression of the lesions. On the other hand, there was no significant relationship established between Cr ions level and the volume, type or the progression of the lesion (p=0.0570, p=0.2221, and p=0.8575, respectively).

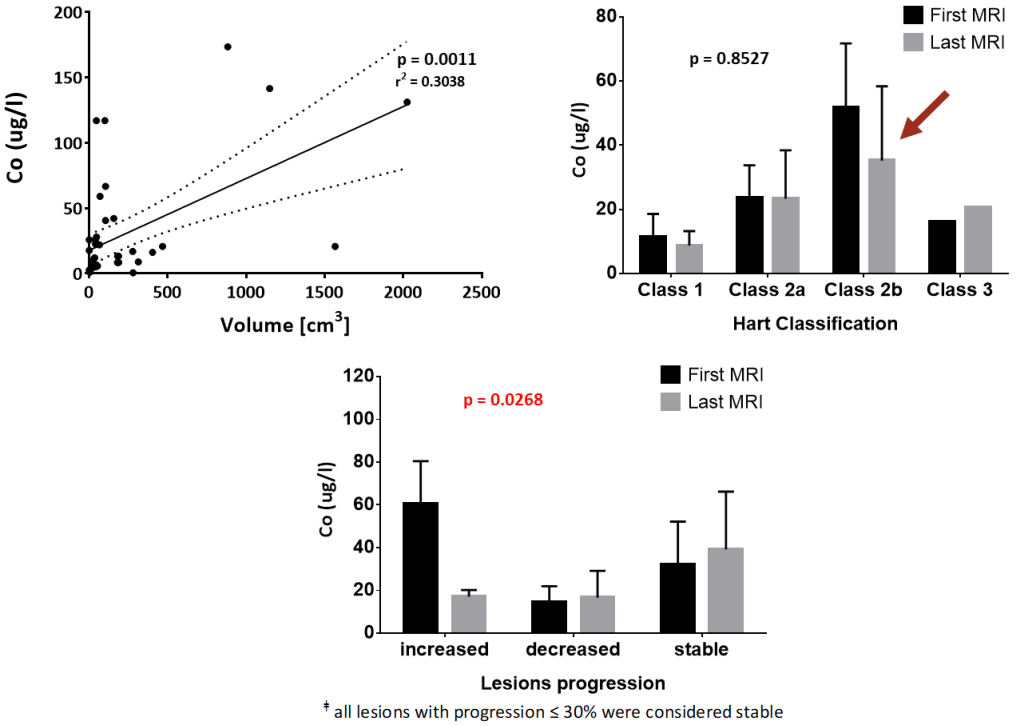

Figure 8. The relationship between the level of Co with the volume and size of progression of the lesions.

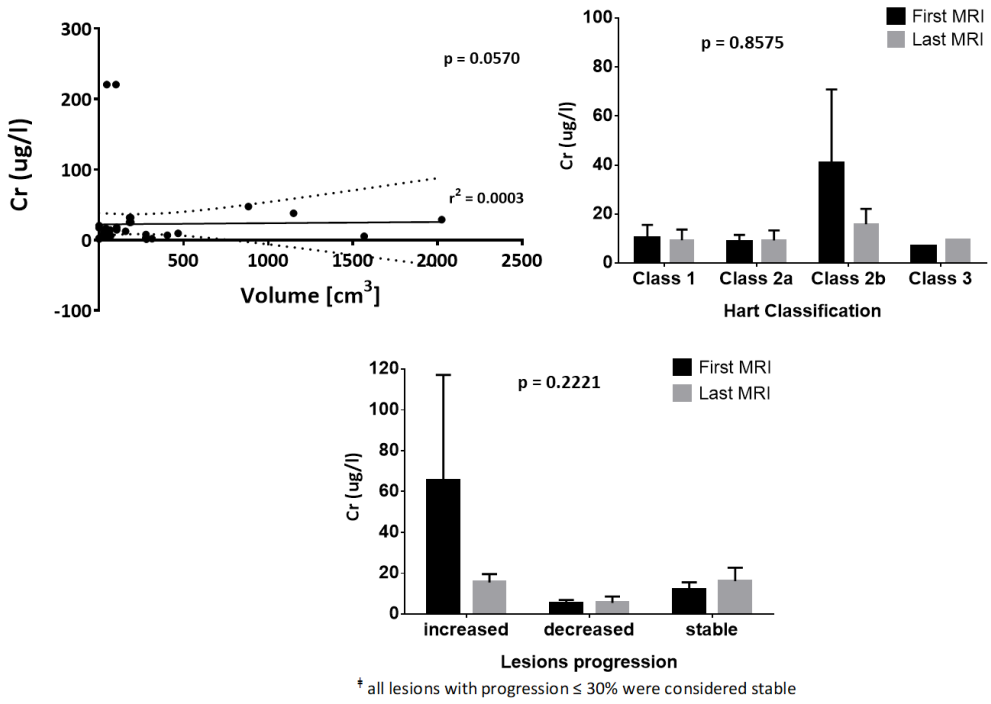

Figure 9. The relationship between the level of Cr with the volume and size of progression of the lesions.

3.1.4. ALTR on sequential MRI and the indications for revisions

Table 2 shows the cases with positive ALTR on sequential MRI and the indications for revisions. On sequential MRI, there were 10 cases (50.0%) which had revision surgery, (7 RHAs, 1 with MoM and 2 with MoP). Of the 10 cases which had revision surgery, 3 were due to a pseudotumor, 2 with femoral neck fracture, 2 with huge lesion and taper corrosion, 1 with aseptic loosening, 1 with a huge lesion, and 1 with huge lesion with dislocation and pelvic discontinuity. Six of the ten cases who underwent revision had increased levels of Co and Cr. Table 3 shows the details of the revised implants.

Table 2. The cases with positive ALTR on sequential MRI and the indications for revisions.

Case No	Sex	Age [years]	Side	Lesion			Blood Metal Ions level			Revised	Cause of revision
				size [cm^3]	clasification 1st MRI	progression‡ last MRI	Cr	Co	change		
RHA 1	F	70	RT	< 5	1	increased	20.4	25.7	decreased		
RHA 2	M	71	LT	< 50	2a	decreased	4.5	6.5	decreased		
RHA 3	F	54	LT	< 50	2b	stable	10.7	10.6	increased	Yes	Pseudotumor
RHA 4	F	61	RT	> 200	3	stable	6.8	16.2	increased	Yes	Femoral neck fracture
RHA 5	M	59	LT	< 100	2a	decreased	12.3	42.1	increased		
RHA 6	M	64	LT	< 100	2a	increased	14.5	40.5	decreased		
RHA 7	F	60	LT	< 5	1	decreased	1.5	2.7	increased		
RHA 8	F	57	LT	< 50	2b	stable	14.4	27.9	increased	Yes	Pseudotumor
RHA 9	M	60	RT	< 5	2a	decreased	3.7	5.1	decreased	Yes	Aseptic loosening
			LT	< 5	2a	decreased					
RHA 10	F	59	RT	< 200	2b	increased	220.4	116.8	decreased		
			LT	< 200	2b	increased				Yes	Femoral neck fracture
RHA 11	F	73	RT	> 500	2b	stable	28.9	131.0	increased	Yes	Huge lesion
RHA 12	M	55	RT	< 50	1	stable	8.3	5.7	stable	Yes	Pseudotumor
			LT	< 50	1	stable					
MOM 1	F	62	LT	> 500	2b	increased	6.1	58.9	decreased	Yes	Huge lesion, dislocation and developed pelvic discontinuity
MOM 2	M	56	RT	> 200	2b	decreased	3.0	17.0	decreased		
MOM 3	M	66	RT	> 200	2b	stable	1.3	0.6	stable		
MOM 4	M	58	LT	>200	2b	increased	3.6	5.7	stable		
COM	F		RT	<100	n/a	decreased					
MOP 1	M	81	LT	> 500	2b	stable				Yes	Huge lesion + taper corrosion
MOP 2	M	84	LT	> 500	2b	increased				Yes	Huge lesion + taper corrosion
MOP 3	F	85	RT		2b	disappeared					

‡ all lesions with progression ≤ 30% were considered stable

Table 3. Causes for revision

Case No	Sex	Age [years]	Side	Lesion			Blood Metal Ions level			Comment	Revised	Cause of revision
				size [cm^3]	clasification 1st MRI	progression‡ last MRI	Cr	Co	change			
RHA 4	F	61	RT	> 200	3	stable	6.8	16.2	increased	Large lesion/ continues to grow after revision	Yes	Femoral neck fracture
RHA 9	M	60	RT	< 5	2a	decreased	3.7	5.1	decreased		Yes	Aseptic loosening
RHA 10	F	59	LT	< 200	2b	increased	220.4	116.8	decreased	Large bilateral lesions / still large after revision	Yes	Femoral neck fracture
RHA 11	F	73	RT	> 500	2b	stable	28.9	131.0	increased		Yes	Huge lesion
MOM 1	F	62	LT	> 500	2b	increased	6.1	58.9	decreased		Yes	Huge lesion, dislocation and developed pelvic discontinuity
MOP 1	M	81	LT	> 500	2b	stable					Yes	Huge lesion + taper corrosion
MOP 2	M	84	LT	> 500	2b	increased					Yes	Huge lesion + taper corrosion

‡ all lesions with progression ≤ 30% were considered stable

.

3.2. Systemic effects

Ten patients were included in the analysis, all without history of any cardiac (normal ECG and cardiac markers) and history of renal conditions. Of the ten patients, 8 (80.0%) were males and 2 (20.0%) were females. The mean age of the patients was 54.90 ± 4.25 years old (range: 49 to 60 years old).

Co levels ranged from 0.72 to 141.4 ug/L (mean of 43.23 ± 57.03 ug/L). Cr levels ranged from 0.89 to 88.3 ug/L (mean of 27.78 ± 34.07 ug/L). The mean BMI was 28.2 kg/m2 (range of 26.7 to 33.0). The mean time from surgery was 12.40 ± 2.17 months (range: 8 – 15 months). There were 4 patients (40.0%) with late gadolinium enhancement (LGE), 5 patients (50.0%) with reduced left ventricular ejection fraction (LVEF), one patient (10.0%) with small left ventricular size, one patient (10.0%) with myocardial hypertrophy, one patient (10.0%) with hypokinesis, one patient (10.0%) with pericardial effusion, 3 patients (30.0%) with myocardial inflammation / edema, and 5 patients (50.0%) with fibrosis. All implants were all in position assessed by x-ray. Table 4 shows the detailed results of all ten patients.

There were no significant correlations between blood Co and Cr levels with the cardiac parameters. There was a significantly positive correlation between the presence of

pericardial effusion with Cr but not with Co. Correlation for LV mass was not computed since all patients had normal findings. Table 5 shows the Pearson correlation results between blood Co and Cr levels and the different cardiac parameters.

Table 4. Cardiac MRI results of ten patients with MoM hip arthroplasty

No	gender	age	time from surgery	Cr (ug/L)	Co (ug/L)	LGE	LVEF	LV size	myocardial thickness	LV mass	wall motion	pericardial effusion	myocardial inflammation / edema	fibrosis
1	male	60	11	88.3	117.8	present	reduced	normal	normal	normal	normal	present	present	present
2	male	54	15	9.36	33	absent	reduced	normal	normal	normal	normal	none	none	none
3	male	58	14	26.7	113.1	present	normal	normal	normal	normal	normal	none	present	none
4	male	60	12	83.1	141.4	present	reduced	normal	normal	normal	normal	none	none	present
5	female	50	12	9.88	11.2	present	normal	normal	normal	normal	normal	none	none	present
6	male	54	15	1.62	4.69	absent	reduced	normal	hypertrophy	normal	normal	none	none	none
7	male	49	11	0.92	0.76	absent	normal	normal	normal	normal	normal	none	none	none
8	male	59	8	0.89	0.72	present	normal	small	normal	normal	normal	none	present	present
9	male	50	14	1.82	1.76	absent	reduced	normal	normal	normal	hypokinesis	none	none	none
10	female	55	12	5.21	7.89	present	normal	normal	normal	normal	normal	none	none	present

LGE – late gadolinium enhancement; LVEF-left ventricular ejection fraction; LV- left ventricle

Table 5. Pearson correlation results between blood Co and Cr levels and the different cardiac parameters

Cardiac parameters	Co Pearson correlation coefficient (p value)	Cr Pearson correlation coefficient (p value)
LGE	0.501 (0.140)	0.489 (0.152)
LVEF	0305 (0.392)	0.435 (0.209)
LV size	-0.262 0.465)	-0.226 (0.531)
Myocardial thickness	-0.237 (0.509)	-0.218 (0.545)
Wall motion	-0.255 (0.476)	-0.216 (0.549)
Pericardial effusion	0.45 (0.182)	0.676 (0.032) *
Myocardial inflammation / edema	0.411 (0.238)	0.321 (0.366)
Fibrosis	0.232 (0.518)	0.455 (0.187)

** significant*

LGE – late gadolinium enhancement; LVEF-left ventricular ejection fraction; LV-left ventricle; Co-cobalt; Cr-chromium

CHAPTER IV. DISCUSSION

4.1. Local effects

In this study, we have shown that the ALTR lesions have the tendency to remain stable for a period of time particularly when they are fluid-filled and small in size. Smaller fluid filled lesions may eventually regress over time and may even disappear. Small lesions (less than 10 cm^3) usually occur in 39% of cystic lesions, and they may be symptomatic or asymptomatic (Fehring et al, 2014). However, whether such ALTR lesion progression is under question particularly in asymptomatic patients, a repeat MRI is warranted. Cystic lesions with wall thickness less than 3 mm were found to be non-progressive and may eventually regress and follow up of these small asymptomatic lesions may not be necessary contrary to other report, but lesions with increased wall thickness and mixed fluid content may have a different story that need follow-up (Kwon et al, 2016).

Fluid-filled lesions and the presence of periarticular fluid collections even in patients who are not in pain was found to be alarming and may put patients at risk for ALTRs (Fehring et al, 2014). On the other hand, larger lesions (>10 cm^3 in size) have greater tendency to create more tissue damage including necrosis. Larger lesions tend to be symptomatic and with higher levels of cobalt ions. This association has explicitly described the association of higher cobalt ion levels with the size of the lesion (Sutphen et al, 2016; Hasegawa et al, 2014) similar to our findings. Sutphen et al (2016) followed up 24 patients and assessed the volume of the lesion using MARS MRI and concluded that the more the bigger the tumor size is, the more it will grow. Furthermore, lesions that have more than 100 ml of fluid has the tendency to invoke further tissue destruction and damage. Thus, a follow-up is necessary with larger lesions since they usually progress to a more advance stage using ARS MRI. In such cases, revision is warranted since the abductor muscles may be damaged, and a posterior approach may be considered.

Of our 10 cases who had revision surgery, three were due to a pseudotumor, and six of the 10 who had revision had increased levels of Co and Cr. This is in agreement with previous studies where follow-up of asymptomatic patients who had pseudotumors (even those that were small and have less than 31 cc. of fluid) continue to grow and advance (Almousa et al, 2013; Bosker et al, 2012). Bosker et al (2012) found out that almost third of the asymptomatic cases were positive for pseudotumors, 10.8 % of which needed revisions for different reasons, whereas those with pseudotumor negative hips had only 4.1% revision rate. Revision of pseudotumors or ALTR were found to have a poorer outcome compared to revision of hip arthroplasty secondary to failure of other etiology (Grammatopolous et al, 2009). However, frequent dislocation, pseudotumor recurrence and acetabular loosening are complications that need to be considered after revision surgery (Liow and Kwon, 2016; Matharu et al, 2014).

Other factors including the size of the prosthesis head have to be considered as elucidated in previous studies, whereby this contributes to the eventual stability of the prosthesis particularly among patients with MoM implants (Whitehouse et al, 2013). Moreover, factors that were found to alter the development of ALTR included pain as a strong predictor for pseudotumor presence (Bosker et al, 2012), the location of the lesion (posterolateral approach) which was found to have a higher incidence of lesions compared to the direct lateral approach (Koziara et al, 2016), cup malpositioning, female gender, clicking sensation and femoral head size (Langton et al, 2010; Kwon et al, 2011; Donnell et al, 2010; Matthies et al, 2011; Saxler et al, 2004; Glyn-Jones et al, 2009; Koziara et al, 2016). More recent studies revealed that including the implant design (Trunnion design), reduced femoral head-cup contact, metal hypersensitivity, low body mass index, and high activity level are also important patient risk factors for wear and local reactions (Liow and Kwon, 2016; Kwon et al, 2010; Matthies et al, 2014).

In studies that used MARS MRI, the more advanced lesions showed tendency to progress to a larger lesion and cause more tissue damage, and only a smaller percentage of those with normal hips progress and have a new lesion on follow-up MRIs (Briant-Evans et al, 2015). Furthermore, high cobalt ion in the blood and irregular pseudocapsule of the lesions on scan were found to be more likely to progress with significant relationship, similar to the findings in this study (Briant-Evans et al, 2015).

In general, we recommend revision early in the disease before the lesions become huge with very poor surrounding soft tissue. One of our cases presented late and he developed multiple dislocation although revision surgery was done many times. The condition of the stabilizing muscle was poor, and the hip is easily dislocated. Late intervention in the disease usually result in poor outcome and more likely to have complications (Grammatopolous et al, 2009). In addition, small lesions with significant progression should be attacked early in the disease before more muscle and soft tissue destruction develop.

4.2. Systemic effects

In attempt to find the effects of circulating levels of Co and Cr in the blood, we found that there were no significant correlations between blood Co and Cr levels with the cardiac parameters. Our findings were not consistent with findings of previous studies where high levels of cobalt were found to be directly linked to heart failure and cardiomyopathy (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015; Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Cheung et al, 2016; Gillam et al, 2017; Moniz et al, 2017). This is probably due to the fact that our patients were essentially normal without history of any cardiac (normal ECG and cardiac markers) and history of renal conditions, and most of the cardiac abnormalities that were seen at a mean of 12 months after hip surgery were reduced LVEF, myocardial hypertrophy, hypokinesis, pericardial effusion, myocardial inflammation /

edema, and fibrosis which may not necessarily mean heart failure and/or cardiomyopathy brought about by the increased levels of Co and Cr in the blood.

Additionally, several reported cardiac toxicity cases brought about by an increased Cr and Co metal ions in the blood occurred 43 months after arthroplasty (Tower, 2010), and our cases were followed up 8 to 15 months only after surgery due to time constraints. Furthermore, three of our cases had elevated blood Co level (>100 ug/L) however, only one of the three cases with elevated blood Co level presented with cardiac failure. This is in disagreement with studies that associated high levels of blood Co (>100 ug/L) to cardiac toxicity (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015). Histopathological findings in Co related cardiac toxicity include myofibrillar hypertrophy, interstitial fibrosis and muscle fiber degeneration (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015).

On the contrary, there were studies that showed that even in the presence of raised serum Co levels of patients who had MOM HA (18-153 ug/L), no cardiac effects may be identified (van Lingen et al, 2013). A more recent study showed that high blood cobalt and chromium levels have no significant cardiotoxic effects on patients with MoM hip implant verified by echocardiography, cardiac MRI and cardiac blood biomarkers (Berber et al, 2017). None of our patients showed muscle fiber degeneration although one patient showed myocardial hypertrophy (but his blood cobalt level was only 4.89 ug/L), in contrast to the findings from previous studies (Mosier et al, 2016; Oldenburg et al, 2009; Dahms et al, 2014; Martin et al, 2015). On the contrary, our study is in agreement with studies that showed no cardiac effects or elevations in the cardiac blood biomarkers even on raised blood cobalt and chromium concentration (van Lingen et al, 2013; Berber et al, 2017), and that a high blood Cr and Co levels (but not extreme values) do not have a significant cardiac effects on patients with MoM hip implants. In fact, we had four patients with high metal ion concentration in the blood

(>100 ug/L) that should have shown significant cardiotoxicity, however there was none. Furthermore, we also had patients who had implants for more than 10 years, and if the duration of the implant has to something to do with cardiotoxicity (as claimed by Qu et al, 2011) and the increasing levels of blood metal ions concentration, our data could have shown it.

With regards to the kidneys, we report a case of a 61-year old who had severe osteoarthritis and who have gone bilateral THA in 2004 (right hip) and 2011 (left hip). Five years after, clinical and laboratory findings showed a high blood C-reactive protein (CRP) of 39.4 mg/L with elevated cobalt (247.8 ug/L) and elevated chromium level (63.9 ug/L). Both implants at that time of follow-up were found to be radiographically stable. Urinalysis revealed marked proteinuria and hematuria. Kidney biopsy, immunofluorescence and electron microscopy studies revealed large mesangial dense deposits and IgA deposits. He was diagnosed with a rare case of new-onset immunoglobulin A (IgA) nephropathy. He underwent revision surgery from MoM to a CoC implant. Surprisingly, at 30 days post-revision, blood metal ion levels dropped significantly to 73.5 ug/L for cobalt and to 20.8 ug/L for chromium. At one-year follow-up after revision surgery, his blood metal ion levels were close to normal threshold and his kidney function improved. This is the only reported case of new-onset IgA nephropathy that was seen in a patient who had MoM-THA, in which blood metal ions of cobalt and chromium significantly dropped after he underwent revision surgery replacing MoM to a CoC implant. There were studies that showed elevation of blood metal chromium and cobalt ions with MoM implants, although there were also studies that reported non-significant elevated levels of these metals and non-elevation of renal markers particularly serum creatinine level and insignificant decrease in creatinine clearance among patients who had MoM hip implants (Corradi et al, 2011; Marker et al, 2007). Median serum creatinine level and median creatinine clearance were found to be comparable to controls and were found to be not associated with metal levels (Corradi et al, 2011). Cobalt or chromium concentrations (median serum cobalt

concentration was 0.75 (0.3–50.10) μg/l and the serum chromium concentration was 0.95 (0.3–58.6) μg/l after following up patients for ten years postoperatively (Marker et al, 2008). However, the renal picture seemed different among patients with existing renal disease. A study showed that the mean serum cobalt concentration was reported to be more than 100-fold higher among patients who have chronic renal failure than in patients with the same prosthesis type and similar follow up period, but with no known renal disease (Hur et al, 2008). It was also reported that the 9-yar risk of developing chronic renal disease after primary THA was 14% and severe or end-stage renal disease to be 6% (Chandran and Giori, 2011). There were reports that claimed that late gadolinium (contrast) enhancement is related to iron or any metal overload in the tissue. Gadolinium-based contrast agents are safe at recommended doses for patients with normal kidney function, however, there has been reports that these gadolinium-based contrast agents can cause nephrogenic systemic fibrosis in patients with renal insufficiency, thus also enhancing the metal overload of toxic ions in the blood (Ramalho et al, 2016; Kanal and Tweedle, 2016). Unfortunately, there were no studies up to this writing that focused on the kidney effects particularly IgA nephropathy except this case that we are reporting. Whether this assumption / finding is true, this remains to be further investigated.

CHAPTER V. SUMMARY OF FINDINGS

With regards to local effects of cobalt and chromium in the blood among patients with MoM hip implants, a higher Hart classification showed a tendency to increase or maintain their sizes compared to those of lower classification. There was a significant positive relationship that was identified between the level of cobalt ions with the volume and size progression of the lesions. However, no significant relationship was established between Cr ions level and the volume, type or the progression of the lesion. Lesions type 2b and 3 have a more aggressive behaviour. Bigger lesions tend to grow, and smaller lesions can regress or can remain stable for a longer time. We think that a small, fluid-filled lesion and larger prosthesis head are the contributing factors for stability. Lesions associated with RHA are more benign and may stay stable for a longer time. ALTRs associated with MoP are rare but are usually aggressive. Furthermore, half of the patients need to undergo revision of MoM bearing implants. Pain is the main indication for revision surgery, but large lesions should be monitored closely. The best time for intervention is before the development of further irreversible tissue damage.

With regards to the cardiac effects of cobalt and chromium ions in the blood among patients with MoM hip implants, our study suggests that there is no correlation between elevated blood cobalt and chromium levels and cardiomyopathy. Individuals with a well-functioning implant are at minimal or no risk of developing cardiac disease. Thus, the absolute presence of elevated metal ions is insufficient to cause cardiac disease on the patient.

CHAPTER VI. RECOMMENDATIONS

This study has shown several implications for further research on this subject matter. Future research can be conducted on a larger sample size and determine the interplay between different factors including age, duration of hip implant, size of the MoM implant, and the levels of cobalt and chromium to the presence of local and systemic effects including the heart, kidneys and the thyroid. Further investigation on the effect of gadolinium-based contrast agents on the accumulation or excretion of these toxic metals and its relation to nephrotoxicity will also shed light on the enhancing effects of gadolinium on the metal overload of chromium and cobalt in the blood of patients who have undergone HA.

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