Metal-on-metal joint bearings and hematopoetic malignancy
A review

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Submitted 12-06-14. Accepted 12-09-27

Abstract **This is a review of the hip arthroplasty era. We concentrate on new metal bearings, surface replacements, and the lessons not learned, and we highlight recent reports on malignancies and joint implants. A low incidence of blood malignancies has been found in bone marrow taken at prosthetic surgery. The incidence is increased after replacement with knee implants that release very low systemic levels of metal ions. A carcinogenic effect of the high levels of metal ions released by large metal-on-metal implants cannot be excluded. Ongoing Swedish implant registry studies going back to 1975 can serve as a basis for evaluation of this risk.**

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Historical considerations

After more than 3 decades of limited success with hemiarthroplasty, the total hip arthroplasty (THA) era started in the 1950s in Europe. In 1953, the McKee 32-mm metal head articulating against a metal cup (MOM) made of cobalt-chromium was introduced (McKee and Watson-Farrar 1966). The success with low-friction arthroplasty (LFA) (Charnley 1961) was a dramatic leap forward, at the start only hampered by deep infections in up to 10% of the cases. At the beginning of the 1970s, strict aseptic and antiseptic routines combined with systemic and local antibiotic prophylaxis reduced the risk of infection to less than 1% (Lidgren 2001, Jämsen et al. 2010).

The initial outcome with the cemented MOM THA was also promising, but early on it resulted in 2 main failure patterns (Benson et al. 1975). Loosening and migration of the acetabular cup occurred due to high friction and impact forces. Secondly, local inflammation around the implant with black-tinted tissue was observed in early revisions for pain, and it was believed to be caused by metal wear particles (Evans et al. 1974). Improved production of the McKee with matched components led to jamming, and increased the failure rate even more. Coleman et al. (1973) reported a 15-fold increase in Cr in urine and an 11-fold increased level of Co in whole blood (Coleman et al. 1973). In addition, Benson et al. (1975) showed a high incidence of metal sensitivity in MOM McKee-Farrar THA compared to metal-to-plastic THA.

In a short-term follow-up of MOM McKee-Farrar THA, revision had been done in 15% of cases at 4 years (Baldursson 1980). Single long-term studies have, however, also reported prosthetic survival in up to 75% of cases at 20 years (Brown et al. 2002). At the end of 1970, the McKee-Farrar MOM concept was abandoned in favor of the LFA concept, which has had a well-documented excellent long-term outcome (Callaghan et al. 2000, Learmonth et al. 2007).

Surface replacement

A partly new idea, the surface replacement (SR), was introduced in 1974 by Wagner in Germany (Wagner 1978). A large (44 mm or more) 3-mm-thick stainless steel cup was placed on the preserved femoral head and a thin polyethylene cup (4–6 mm) was inserted in the acetabulum. As early as the 1930s, the same concept—but as a mold hemiarthroplasty—had been introduced, first made of glass but later made of stainless steel (Smith-Petersen 1948). The joint-preserving SR method quickly became popular, especially in active young patients, reducing the risk of dislocation. But soon afterwards, new complications were reported, i.e. cervical neck fractures due to several factors such as femoral notching and loosening of the femoral cup secondary to bone necrosis (enhanced by particles and circulatory disturbances). In addition, the thin polyethylene acetabular cup was deformed and it added to a high early failure rate (Mogensen et al. 1982). A long-term study of the original Wagner SR showed that after 22 years, only 11 of 270 patients still had this prosthesis left in situ (Costi et al. 2010). In 16% of the revisions, loosening was only found on the femoral side. Until the start of the new millennium, the SR method had a strong foothold in the USA (Amstutz et al. 1998).

Metal on metal

It was expected that when the MOM THA concept was revisited by Weber in Switzerland in the 1980s (Weber 1996, Randelli et al. 2012)—and followed in the 1990s by the Birmingham MOM SR in the UK (Carrothers et al. 2010)—that some of the earlier observations and experience of outcome during the previous 70 years had been taken into consideration. The new cobalt-chromium MOM joint bearings were tested tribologically by wear-simulator testing and were claimed to overcome the high friction and wear seen earlier with the McKee-Farrar MOM THA. The risk of femoral neck fracture and loosening were expected to diminish with surgical training using a more gentle technique and better instrumentation.

The initial early success reported by Daniel et al. already in 2004 resulted in a number of "generic" MOM SR prostheses being quickly released by competing companies; these were based on a predicative 510 K process, starting from the BHR approval in May 2006 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080189.pdf). At the same time, several MOM THAs made of cobalt-chromium were reintroduced with the same claim that the new high-precision production methods should give less friction than the LFA. In the USA in 2009, approximately one third of the hip joint procedures were large MOM articulations (Bozic et al. 2010).

Based on the data available today, it is possible to conclude that, except for there being less dislocation with a larger head, none of the claims have come true. For some of the new implants with minimal clearance between the larger metal components, this has resulted (as before) in jamming from local polar edge contact, with wear and increased blood metal ion levels if perfect positioning is not achieved (De Haan et al. 2008, Langton et al. 2008, Hart et al. 2009). There have been no clinical studies verifying the importance of lubrication and optimal clearance between the bearing surfaces for new implant designs.

There is still an increased risk of early revision, of 1.5–3%, for femoral neck fractures with MOM SR (Steffen et al. 2009). Isolated femoral complications could be expected to increase further with time from age-related fragility, accelerated stress shielding, and particle reaction—especially in women with a small neck-to-head ratio.

Metal wear and particle release is a major issue with the new larger bearings, despite the improved tribology verified on the bench. Shedding of large amounts of particles may occur, leading to painful local inflammation and reoperation (Smith et al. 2012). About one trillion small nanoparticles are released in a year in a MOM bearing, which is 14,000 times more particles than with an LFA articulation (Daniel et al. 2012). Recent studies have shown that in patients with well-functioning implants, the average serum levels of Co and Cr are 1–2 µg/L. Levels of up to 387 µg/L for Co and 179 µg/L for Cr have, however, been found. Very high levels in the fluid surrounding a MOM THA have been measured: up to 400 mg/L of Cr and up to 22 mg/L of Co (Sampson and Hart 2012, Srinivasan et al. 2011). In a MOM THA with a modular morse-taper head-neck junction, with metal-on-metal contacts and possible corrosion, the particle release may be even higher (Meyskens and Yang 2011).

Large aggregations of lymphocytes, so-called pseudotumors, in asymptomatic patients studied with ultrasound have been reported in as many as one third of them operated with a MOM THA (Williams et al. 2011, Wynn-Jones et al. 2011). Technical aspects of performing MRI after hip arthroplasty were reviewed recently (Hayter et al. 2012). In a recent registry study from the UK, a clinical failure rate up to 6% in females was found at 5 years for MOM THA (Smith et al. 2012b). The authors reported less revisions with smaller MOM THA articulations, but the rates were still significantly higher than for the metal-on-plastic LFA.

There are significant differences between metal-on-metal concepts, and it might be unfair to lump them together. Excellent results have been reported with the Pinnacle MOM prosthesis, for example, with 98% survival at 7 years (Kindsfater et al. 2012).

That the ASR MOM SR with a less hemispherical cup design is a clear outlier was first reported in Australia (De Steiger et al. 2011), but during the last 2 years several other MOM hip prostheses with large joint bearings have been withdrawn. There has been company-initiated post-marketing surveillance, with patients being informed, and also largely in cooperation with the orthopedic profession. Very recently, the problems have also been taken up by a few regulatory bodies. The lack of international coordination and the need for an independent alert system has been emphasized in 3 successive articles (Langton et al. 2008, Cohen 2011, Heneghan et al. 2012).

Malignancy and metal ion release

A recent concern has been whether the large amount of cobalt and chromium nanoparticles released could cause cancer (http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON143784).

The most relevant systems and organs that might be affected in the medium term (the first 10–20 years) are the hematopoietic system, the urogenital system, and the skin. In the long term (20–40 years), the solid organs might be affected (Little 2009).

By cross-checking of hospital data with national cancer databases, it would be possible to obtain information on increased risk. This has been done with some consistent results on hematopoietic tumors, but with less convincing data on other tumors except prostate cancer and melanoma (Lewold et al. 1996, Lidgren 2008, Wagner et al. 2011). Often, rheumatoid arthritis (with a higher risk of tumor development) is not differentiated from OA; with information taken from hospital systems, this raises some concern about the reliability of the data from the studies already published. A recent short-

term study (Smith et al. 2012a) using the NHS joint register and hospital data from England and Wales found no overall increase in solid and hematopoetic cancer, and also no differences comparing LFA with MOM SR and MOM THA. The median observation time was only 2.8 years, and there was no differentiation between RA and OA.

The specific increase in hematopoetic tumors has recently been verified in a long-term follow-up in a joint replacement registry for patients who received knee prostheses for RA but—never before reported—for OA (Wagner et al. 2011). The release of metal in a metal-to-polyethylene knee joint (TKA) could be expected to be higher than for an LFA because of a bearing contact area that is 10 times greater. The wear patterns in the knee joint are well described, and result in larger plastic particles than those produced in prosthetic hips (Blunn et al. 1992, 1997, Goodman and Lidgren 1992). Co-Cr levels have been reported to be comparable to those with well-functioning MOM THA with a small head, and to be only slightly elevated than those for LFA (Luetzner et al. 2007, Garrett et al. 2010). Several studies have, however, shown higher levels in hinged or semiconstrained TKA (Liu et al. 1998) and loose TKA (Sunderman et al. 1989, Liu et al. 1998).

Several authors have reported an increase in melanoma after joint prosthetic surgery (Nyren et al. 1995, Onega et al. 2006, Visuri et al. 2006, Wagner et al. 2011). It is reasonable to suspect that this is caused by higher long-term exposure to chromium released from the implant. Hexavalent chromium especially has a profound effect on melanocytes at low levels (Meyskens and Yang 2011). In future, the use of X-ray synchronization radiation methods may allow measurement of chromium in single cells (Bohic et al. 2008). This should be studied in more detail in MOM joints that shed a large amount of smaller particles. It might be time to start discussing whether actively giving advice on sun protection to patients with large MOM bearings and high serum levels of chromium is indicated. Development of novel UV-activated chromium-protective chelators was suggested for melanoma prevention not related to joint implants before the MOM era (Yiakouvaki et al. 2006).

Regarding the urogential tract, our earlier findings of a slight increase in prostatic cancer (Wagner et al. 2011) have recently come into focus after unexpected findings of epithelial precancer in the bladders of MOM THA patients; this was reported at the British Hip Society meeting in 2012 (Maclean et al., unpublished observations). An additional study with longer follow-up, reported at the same BHS meeting, found, however, that there was no increase in urogenital malignancies (Kumar et al., unpublished observations). Thus, these findings must be verified statistically and confirmed epidemiologically before any association between an implant and urogenital malignancy can be considered.

Joint disease and tumor

It is well known that inflammation influences tumor develop-

ment. This is evident in a number of inflammatory musculoskeletal conditions such as RA, Sjögren's syndrome, and SLE. An increased risk has been seen for lymphatic tumors especially (Solomon et al. 2012). Interestingly, anti-inflammatory steroid treatment in RA reduces the risk of developing lymphoma (Hellgren et al. 2010). It has been postulated that it is the severity of inflammation and duration of the rheumatoid arthritis that contributes to the increased risk of lymphoma (Askling et al. 2009). The risk of hematological cancer is higher in younger RA patients (Chen et al. 2011).

There is also evidence that patients with seronegative arthritis have an increased risk of developing myelodysplastic malignancies (MDS) (Chandran et al. 1996). In smaller patient series, blood malignancies (i.e leukemia and lymphoma) have been diagnosed in patients who have developed osteonecrosis (Kozuch et al. 2000). The immunological and thrombogenic malignant cascade that results in impaired circulation and therefore osteonecrosis is only partially understood.

The question is therefore whether osteoarthritis could also initiate and drive hematopoietic malignancies irrespective of the implant intervention. At replacement surgery, in advanced cases we often find inflammation and large subchondral cysts filled with fluid and hypertrophic synovial tissue.

As part of bone bank routines, between 1994 and 2005 a Dutch group investigated 852 donor femoral heads for malignancies, using histology. They found unexpectedly that 14 (1.6%) had malignant cells indicative of low-grade B cell lymphoma (Zwitser et al. 2009). At a follow-up after an average of 7 (1–12) years, 2 of the donors had developed active disease and 3 more were being followed up by an oncologist because of suspected disease. None of the recipients who accidently received a low-grade lymphoma bone transplant had developed an MDS malignancy.

In a recent large study of 6,161 osteoarthritic femoral heads donated for transplantation in Perth, Australia, 19 patients had an unexpected neoplasm in the femoral head, 9 of which had systemic disease on further investigation; all of them were hematologic malignancies. Thus, 1 verified malignancy in 770 femoral heads was found. This is much lower than in the Dutch study, but in addition 45 femoral heads had a nodular lymphocyte infiltration and plasmocytosis was found in 10 femoral heads (Mackie et al. 2011). This is similar to the findings by Palmer et al. (1999), with 3 malignancies in 1,146 femoral heads.

It was suggested in the paper my Mackie et al. (2011) that routine histology of the removed bone should be carried out in all joint replacements, and that this would be a cost-effective routine for screening for blood malignancies. The ethical implications of how to handle the finding of malignancy in a donor have not been discussed in the literature.

Lymphoid aggregation is accidently found in bone marrow at post-mortem studies, and increases with age. The distinction between benign reactive aggregates and well-differentiated lymphoma may be difficult, and it is also unclear whether

and how a tumor transition in OA takes place, probably driven by inflammation.

The findings in the Australian, Dutch, and UK studies were similar regarding lymphoma, myelodysplasia, and myeloproliferative lymphoid aggregations. It is important that one third of the indolent local blood malignancies found in the Dutch study over an observation period of less than 10 years developed an overt systemic blood disease.

Does a joint implant drive malignancy in blood?

One remaining concern is whether a specific joint implant will accelerate and/or start tumor development over a longer period of time.

As mentioned, it has been clearly shown that it is possible to have an indolent local malignancy in the bone marrow adjacent to an osteoarthritic joint. In cases of resection of the joint, i.e. on total joint replacement and if the tumor is only located adjacent to the joint, this might prevent tumor development. Whether or not this will have any influence on the MOM SR concept is unclear, and it is unlikely considering the generalized nature of MDS and lymphoma. All the published long-term studies on small MOM bearings and hematological malignancies have been on total joint replacements where the proximal and distal parts of the joint have been resected, i.e. McKee-Farrar THA. Due to the vast amount of large MOM bearings inserted in the USA and the UK, this should be analyzed continuously and needs to be followed in the long term. Pooling and aggregation of the available ongoing MOM registry data from several countries is possible, but complicated because of data-protection laws. However, cross-checking of joint registries with the national cancer registries is warranted.

As an extension of our and others' earlier published studies (Lewold et al. 1996, Lidgren 2008, Mackie et al. 2011, Wagner et al. 2011), we compared the incidence of hematological malignancies taken from the national cancer database in Sweden, bone biopsy tumor findings from the large Australian Hip OA cohort, and data from OA patients in the prospective national knee prosthetic register cohort in Sweden (going back to 1975 and covering all clinics). The aim was therefore to determine whether there has been—in addition to the baseline level of malignancies seen in bone marrow at primary prosthetic replacement—a long-term increase in blood malignancies related to joint implants releasing low levels of metal particles. This could give some indication of the follow-up necessary for MOM bearings releasing several orders of magnitude higher levels of metal ions.

Assuming that the disease duration of hematological malignancies was equal in the Australian and Swedish knee cohorts, an approximate annual incidence of 31/105 could be calculated using the prevalence of indolent blood malignancies in femoral heads taken from the large Australian study (De Steiger et al. 2011). This is almost the same incidence as was observed using data from the Swedish study (Wagner et al. 2011) in the 10 years prior to knee replacement: 34/105. After

surgery, the Swedish incidence of blood malignancies was 137/105 (unpublished data). The corresponding incidence in the general population of Sweden, had it had the same sex-, age-, and calendar-year distribution, would have been 81/105 before the operation and 122/105 afterwards. Part of this increase in incidence may have been due to changes in the cohort's distribution of age, sex, and calendar year.

Furthermore, the low preoperative incidence level may have been affected by the fact that the preoperation cohort was a selected population, as it is likely that it included healthier individuals than in the general population, with respect to hematological malignancies. Consequently, the most severe cases were automatically excluded. In addition, patients with multiple diseases and in poor condition because of comorbidities may have been prevented from having surgery, thereby excluding them from the preoperative knee cohort.

However, irrespective of whether the increase was caused by other confounding factors such as frequent radiation exposure and virus infection, or indeed metal exposure, these data can be seen as a baseline reference for an extended follow-up of large MOM bearings.

The blood malignancies diagnosed in the bone marrow at prosthetic replacement could not fully explain the low but clear increase found after long-term knee replacement. We therefore propose that the pre-existing condition of lymphoid aggregates in OA may be further activated by metal ions after implantation. Depending on the stage of the condition, the combination of OA pathology in bone marrow and the reaction to metal ions after implantation can contribute to the development of the blood malignancies.

http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON143784.

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080189.pdf

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