Background
BACKGROUND

1. To determine the mid and long term clinical outcome of cemented 28mm metal-on-metal THA in comparison with metal-on-polyethylene THA

The resistance to wear shown by some designs of metal-on-metal THAs after two decades in situ encouraged the re-introduction of the metal-on-metal bearing. Adjustments in metallurgy, sphericity and radial clearance were incorporated to create second generation metal-on-metal arthroplasties in the late 1980’s. A consensus symposium in 1995 attributed the early failures of first generation metal-on-metal designs to suboptimal surgical technique, excessive or negative clearance, poor fixation and neck/socket impingement. Key factors for long-term success were deemed a polar bearing, sufficient clearance, avoidance of impingement and adequate fixation. Second-generation metal-on-metal wear rates were reported to be 20 to 100 times lower than conventional polyethylene wear rates.

The literature at the time of conception of our studies supported favorable clinical results and acceptable mid-term survival of second generation cementless metal-on-metal THAs. Lombardi et al. reported the 5-year results of 99 patients, comparing 53 cementless metal-on-metal to 46 metal-on-polyethylene THAs. Survival rate was 100% at 5.7 years in both groups, and no radiological or clinical differences were noted between the groups. Others showed equal clinical and radiological performance of 18 cementless metal-on-metal THAs compared to 23 metal-on-polyethylene THAs in a randomized controlled study. After a mean follow-up of 3.2 years, survival was 100% in both groups. Jacobs et al. reported good clinical results and equal radiological outcome in 95 metal-backed metal-on-metal THAs compared to 76 metal-backed metal-on-polyethylene THAs.

Although cementless metal-on-metal THAs showed promising short-term results, much less evidence was available on the outcome of cemented metal-on-metal prostheses. Dorr et al. implanted 70 Metasul metal-on-metal articulations with a cemented Weber cup and cementless or cemented stems. Survival was 98% at an average of 5.2 years in 56 patients. At follow-up, average Harris hip score was 90 points; no acetabular osteolysis was seen, but calcar resorption was noted in two hips. Levai et al. calculated a 94% survival but noted a high number of radiolucencies in 122 Metasul metal-on-metal THAs at an average of almost 4 years follow-up.

In summary, in spite of favourable mid-term clinical outcomes, metal-on-metal THAs had not shown clinical superiority over metal-on-polyethylene yet. Furthermore, long-term randomized controlled trials were absent, especially for cemented metal-on-metal
prostheses. For this reason, we formulated the first aim of this thesis: to evaluate the 5-year and 10-year clinical outcome of a cemented 28mm metal-on-metal THA, in comparison to a cemented 28mm metal-on-polyethylene THA, using a randomized trial.

2. To determine the short term clinical outcome and periprosthetic bone implications of cementless large femoral head metal-on-metal THA in comparison with metal-on-polyethylene THA

Proposed benefits of metal-on-metal articulations were a reduction of wear, a subsequent lower incidence of periprosthetic osteolysis and eventually improved prosthetic survival. Clinical studies showed good clinical results and acceptable prosthetic survival\textsuperscript{6, 7, 8, 11} but with respect to osteolysis, some studies found unexpected early osteolysis\textsuperscript{12}, whereas it seemed almost none-existent in other studies.\textsuperscript{13, 14} Since osteolysis is implicated in the early phases of prosthetic loosening and failure, it is essential to accurately quantify periprosthetic osteolysis. Conventional radiology is not sensitive and accurate enough to detect small amounts of bone loss, but DEXA is able to detect even small defects in the periprosthetic bone in the acetabulum.\textsuperscript{15} For the patient, DEXA results in less radiation exposure than CT.

To our knowledge, no study had quantified periprosthetic acetabular bone changes around metal-on-metal bearings, let alone in a randomized trial. The clinical importance of periprosthetic osteolysis and the widespread use of large femoral head metal-on-metal total hip arthroplasty led us to formulate our second objective: to set up a randomized clinical trial to evaluate the clinical outcome, periprosthetic acetabular bone density, and serum metal ion levels of cementless large femoral head metal-on-metal THA, in comparison to cementless 28mm metal-on-polyethylene THA.

3. To assess the effect of large femoral head THA on range of motion and to study heterotopic ossification as a factor that can compromise range of motion

Metal-on-metal bearings allowed the use of thinner acetabular components and larger femoral heads, with potential advantages of greater range of motion and less risk of dislocation. Meanwhile, hip simulator and retrieval studies had shown that large femoral heads were also favorable for wear: wear rates decreased with increasing head size >40mm, low radial clearance (120-200 μm) and high carbon content (0.2-0.3%).\textsuperscript{16} Large femoral heads increased range of motion (ROM) in hip simulator and biomechanical studies\textsuperscript{17} and a large head-neck diameter ratio might be the crucial factor for obtaining large ROM.\textsuperscript{18}
Clinical hip ROM after large femoral head hip resurfacing arthroplasty, in comparison to conventional THA, was described in only a few reports. One randomized blinded study compared hip resurfacing to THA, but showed no differences in postoperative ROM.

One of the factors that may compromise range of motion after THA is the formation of heterotopic ossifications (HO). The incidence of HO varies from 8% to 90% depending on risk factors and the criteria used. Especially advanced stages of HO, Brooker grades 3 and 4, are clinically relevant because of pain and hip function impairment. Pulsed lavage around the hip joint and gluteal muscles may prevent HO, is inexpensive and has no known side effects. Only one study on the effect of pulsed lavage has been published and suggested no protective effect on HO formation. In this study, however, all patients received lavage; pulsed or manual with a syringe.

In summary, the clinical benefit of a large femoral head THA in terms of range of motion was still unclear. Hence, we formulated the third objective of this thesis: to evaluate the clinical range of motion after large femoral head THA, in comparison to 28mm THA, using a randomized trial. In addition, we aimed to evaluate the incidence of heterotopic ossifications after cementless THA with and without peroperative pulsed lavage.

4. To study the effects of cobalt and chromium ions on osteoblast cells in-vitro.

As metal-on-metal bearings wear, they generate metal particles, mainly cobalt and chromium. Contrary to the micrometer-sized particles of metal-on-polyethylene bearings, metal-on-metal generated particles are nanometer-sized. These smaller metal particles caused less granulomatous inflammation histologically but were produced in larger numbers, hence contributing to an even larger collective metal burden. These nanometer-sized metals have the potential and tendency to corrode if dissolved in solutions such as the synovial fluid, and form metal ions, for instance cobalt and chromium. Particles larger than 0.1 μm are generally cleared from the joint by macrophages, but nanometer-sized particles and ions are unlikely to stimulate phagocytosis by macrophages. It is well known that metal-on-metal hip arthroplasty gives rise to elevated metal ion levels locally in the synovium, but also distally in the serum and urine. There is no agreement on what level of local or systemic cobalt and chromium ion concentration is normal, let alone acceptable. These ions can be measured in serum and in whole blood and a consensus meeting suggested serum would be preferable. Inductively coupled plasma mass spectroscopy (ICP-MS) and graphite furnace atomic absorption spectrophotometry (GFAAS) are the most commonly used methods. Because of the tendency for outliers in metal ion measurements, the median value is
preferred over the mean. An overview paper lists 12 studies on serum or whole blood metal ion levels in different metal-on-metal total hip arthroplasties, ranging from 0.7 to 2.3 μg/L for cobalt and 1.0 to 2.5 μg/L for chromium, with a maximum follow-up of 5 years. Other authors review 8 studies on median serum or whole blood ion levels with various metal-on-metal hip resurfacings; these levels ranged from 0.5 to 4.3 μg/L for cobalt and 0.9 to 5.1 μg/L for chromium, with a maximum 2 year follow-up. Cobalt and chromium levels are influenced by the type, design, and positioning of the implant, with malpositioned (steep) cups showing higher levels; the effects of femoral head size remain controversial, although steep cups combined with small femoral heads seem at risk.

Measurement of serum cobalt and chromium concentrations has been advocated as a monitoring tool for high wear rate induced failure of metal-on-metal bearings. In revised metal-on-metal arthroplasty patients, systemic cobalt and chromium ion levels correlated strongly with hip synovial fluid cobalt and chromium ion levels; the latter were approximately 40-50 times higher. In addition, both serum and synovial ion levels correlated strongly to femoral component wear and serum levels above 17-19μg/L were more often associated with intra-operative metallosis.

Biologic effects of cobalt and chromium ions

There are concerns over the long-term biologic effects of metal wear debris and metal ions. These relate to chromosomal damage, possible carcinogenesis, effects on the fetus in women of childbearing age, metal allergy/sensitivity and metal-induced toxicity including bone loss. Chromosomal aberrations have been described in patients with both metal-on-polyethylene and metal-on-metal arthroplasties. Chromosome translocations and aneuploidy (chromosome gain and loss) were increased in systemic lymphocytes of patients with a metal-on-metal THA. This correlated with molybdenum, but not with cobalt and chromium levels. High levels of chromium in the urine can possibly induce metaplasia of the bladder, as industrial exposure to chromium in metal workers showed an increased bladder cancer risk. In spite of concern for carcinogenesis, there is still no confirmed case of implant-induced cancer, and cancer risk appeared not increased after total hip arthroplasty.

Women of childbearing age have been recipients of metal-on-metal arthroplasties. Two reports have shown that metal ions do pass the placenta and the placenta seems to act as a barrier with lower ion concentration in the umbilical cord blood or serum than in the maternal blood resp. serum. Several children have been born to mothers with metal-on-metal bearings, but to date these children have been apparently normal.
and there are no published incidents. Nonetheless, these studies were all based on mothers with normal functioning implants and relatively ‘normal’ cobalt and chromium ion concentrations, i.e. <2.5 μg/L. Whether or not elevated maternal and fetal metal ion levels are harmful to the fetus is still unknown. Brodner et al. reviewed the literature on cobalt and chromium teratogenicity in humans and found no evidence for this. Novak et al. reviewed animal (rodent) studies and found fetotoxicity of high doses of hexavalent chromium, but not of trivalent chromium or cobalt.

Metal allergy or sensitivity as a cause for periprosthetic soft-tissue changes is considered as a type-IV delayed-type hypersensitivity reaction driven by T-lymphocytes. Even in low metal wear conditions, a small (1%) number of patients may suffer from this type of allergy or hypersensitivity. Our clinic has reported similar observations in the past. The matching histologic features of the joint tissues have been described as aseptic lymphocytic vasculitis-associated lesions (ALVAL), referring to infiltrates of lymphocytes, often with plasma cells and frequently arranged perivascularly. It is uncertain whether ALVAL is only specific for metal-on-metal implants, but in comparison to polyethylene wear debris, Others showed more lymphocytes and plasma cells and less macrophages in periprosthetic tissues of metal-on-metal bearings. The shift from macrophage-induced to lymphocyte-induced reactions with metal-on-metal implants is supported by others. Reduced leucocyte and myeloid cell numbers were shown in blood of patients with a metal-on-metal THA compared to healthy controls and CD8+ and CD4+ T-cell numbers were negatively affected postoperatively. Another group also found reduced lymphocyte numbers, for CD8+ T-cells especially. B-cell and natural killer numbers did not change. Of note, no reduction of CD8+ cells was seen if combined cobalt and chromium levels were less than 5μg/L. Metal-induced lymphocyte reactivity was found to correlate positively with systemic cobalt and chromium ion levels in metal-on-metal patients in another study. To date, there is no reliable standardized predictive test for metal allergy or hypersensitivity.

Potential toxic effects of larger metal particles on various cell types have been studied extensively in the past, but effects of metal ions are less clear. Toxicity, proliferation and viability of osteoblasts, fibroblasts and lymphocytes have been studied in vitro after exposure with different orthopaedic metals in solution. Cobalt and vanadium were found to be toxic, chromium less so, at concentrations clinically likely to be found in synovial fluid.

Effects of cobalt and chromium ions on bone
Only limited studies have investigated the effects of cobalt and chromium ions on osteoblasts and osteoclasts specifically. The results are mixed. Wang et al. investigated the effects of cobalt, chromium and titanium on human osteoblast-like cells at concentra-
ions up to 100μg/L. They found no influence on cell growth, viability and injury after 72 hours incubation. Fleury et al. studied the effects of rather high levels of cobalt ions (0-10ppm, i.e. 0-10000μg/L) and chromium ions (0-150ppm, i.e. 150000μg/L) on MG-63 osteoblasts in-vitro. Osteoblast cell count decreased in a time and dose-dependent manner, with cobalt more toxic than chromium. Cell viability decreased in the presence of cobalt and chromium ions. Markers of oxidative stress (oxidized and nitrated proteins) revealed time and dose-dependent changes, as did the expression of antioxidant enzymes. On the other hand, others found no significant cytotoxicity of chromium ions in osteoblasts (5-20microM). Cobalt ions (10000μg/L) and chromium ions (10000μg/L) added to mature rabbit bone osteoclasts did not induce osteoclast apoptosis, but decreased their size.

A fundamental factor governing bone metabolism by controlling osteoclast formation is the interplay between receptor activator of nuclear factor kappaB (RANK), RANK-ligand (RANKL) and osteoprotegerin (OPG). RANKL, on the surface of the osteoblast, interacts with RANK on the surface of osteoclast precursor cells and stimulates differentiation into mature osteoclasts. RANKL treated mice show increased bone resorption. OPG decreases the number of osteoclasts and mice treated with OPG exhibit lowered osteoclast activity and increased bone volume.

RANK and RANKL play an important role in periprosthetic osteolysis. Both RANK and RANKL were strongly expressed by multinucleated cells containing polyethylene wear debris in hip revision tissues, whereas control tissue stained weakly. A strong correlation was found between RANK, RANKL, volume of bone loss (on CT) and polyethylene wear debris. Polyethylene particles implanted in mice also exhibited high RANKL to OPG ratio’s and extensive osteolysis.

In summary, cobalt and chromium ions can have various biological effects. In clinical practice, preventing osteolysis and subsequent loosening after total hip arthroplasty is probably the most important remaining challenge for hip surgeons. Therefore, the effects of metal ions on osteoblasts and osteoclasts are essential. The literature showed that cobalt and chromium ions affect osteoblasts, but only in very high concentrations. Whether or not osteoblasts are affected by cobalt and chromium ions at the concentrations found in patients clinically, is less clear. Furthermore, it is not known whether cobalt and chromium ions influence the osteoblast expression of RANKL and hence the interplay between RANKL, RANK and OPG. Therefore, we formulated the fourth objective of this thesis: to evaluate the effects of cobalt and chromium ions on human osteoblast-like cells in-vitro.
REFERENCES


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