Hip Resurfacing Arthroplasty

Evaluated by a Meta-Analysis, Microdialysis, Laser Doppler Flowmetry, RSA, DXA, MRI, X-ray and clinical follow-up

PhD thesis

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Preface

This thesis is based on the following papers:

I. Lorenzen ND, Stilling M, Ulrich-Vinther M, Birke-Sørensen H, Søballe K. "Inferior survival of Hip Resurfacing Arthroplasty Compared to Cementless Total Hip Arthroplasty. A Review & Meta-Analysis ". Manuscript submitted to Hip International.

II. Lorenzen ND, Stilling M, Ulrich-Vinther M , Trolle-Andersen N, Prynø T, Søballe K, Birke-Sørensen H. "Increased Ischemia in the Femoral Head Found by Microdialysis by the Posterior Surgical Approach. A Randomized Clinical Trial Comparing Surgical Approaches in Hip Resurfacing Arthroplasty". Manuscript submitted to Acta Orthopaedica.

III. Lorenzen ND, Stilling M, Jakobsen SS, Gustafson K, Søballe K, Baad-Hansen T." Marker-based or Model-based RSA for Evaluation of Hip Resurfacing Arthroplasty? A Clinical Validation and 5-year Follow-up." Manuscript in preparation.

IV. Lorenzen ND, Baad-Hansen T, Jakobsen SS, Gustafson K, Egund N, Søballe K, Stilling M. "Clinical Results and Patient Satisfaction in Hip Resurfacing Arthroplasty Compared to Total Hip Arthroplasty. A 5 year Assessment with Questionnaires, MRI and DXA". Manuscript in preparation.

Contents

Definitions

Aseptic loosening	mechanical loosening of an implant not related to infection
Avascular osteonecrosis	necrosis of the bone tissue caused by interrupted blood supply
Bone mineral density	referring to the amount of mineral matter per square centimeter of bone
Brooker Classification	classification system used to grade para-articular ossifications around hip implants
Circadian rhythm	refers to a 24-hour cycle in biochemical, physiological, or behavioral processes.
Flux Units	arbitrary unit expressing the blood flow measured by laser Doppler flowmetry
Hypoxia	a condition in which the body as a whole or region of the body is deprived of an adequate oxygen supply
Ischemia	absolute or a relative shortage of the blood supply to an organ, resulting in decreased delivery of oxygen and glucose.
Laser Doppler flowmetry	technique used to monitor blood flow and perfusion of tissues, by the use of laser lights
Metabolism	chemical reactions inside the cells of living organisms, divided into; catabolism: the breakdown of organic matter to produce energy and anabolism: the use of energy to construct components of cells.
Osteolysis	resorption of bone tissue surrounding hip implants caused by joint disease or infection
Pseudotumor	term used to describe soft-tissue lesions surrounding hip implants with metal-on-metal articulations. The lesions are not related to cancer and can be cystic as well as solid.
Radiolucent lines	linear areas of osteolysis in the bone surrounding orthopedic implants
Stress shielding	refers to the reduction in bone density (osteopeni) as a result of removal of the normal stress from the bone by an orthopedic implant

Wolf´s law	states that the bone in a healthy person or animal will remodel in response to the loads which it is placed under.

Abbreviations

AntLat	Antero-lateral surgical approach
BMD	Bone mineral density
$C_{glucose,\ lactate,\ pyruvate,\ glycerol}$	Concentration of glucose, lactate, pyruvate, glycerol
DXA	Dual-energy x-ray absorptiometry
FU	Flux Unit
Glu	Glucose
Gly	Glycerol
HRA	Hip resurfacing arthroplasty
Lac	Lactate
LDF	Laser Doppler flowmetry
L/P ratio	Lactate/pyruvate ratio
L/G ratio	Lactate/glucose ratio
MD	Microdialysis
MOM	Metal-on-metal bearing material in hip arthroplasty
MOP	Metal-on-polyethylene material in hip arthroplasty
MRI	Magnetic resonance imaging
PET	Position emission tomography
Post	Posterior surgical approach
Pyr	Pyruvate
RCT	Randomized clinical trial
RSA	Radiostereometric analysis
THA	Total hip arthroplasty

1. English summary

Osteoarthritis is a disabling condition resulting in pain, decreased range of motion and impaired function. The treatment of end stage osteoarthritis is a replacement of the hip joint by an implant and more than 9000 hip implants are inserted each year in Denmark. The survival of hip implants is acceptable in patients above 75 years of age at time of surgery, whereas patients aged 50 years or younger have a revision risk of 20% within 10 years. Younger patients bear a higher risk of revision due to a higher level of activity and hence more wear on the implant.

Wear on an implant results in the formation of wear-particles, depending on the implant material, with metal or polyethylene being the most common. Polyethylene wear-particles are associated with aseptic loosening of hip implants, which requires revision of the implant. Furthermore, during revision surgery of traditional stemmed hip prostheses, it is necessary to remove additional bone stock from the femoral canal which increases the risk that the new implant will not be optimally fixed to the femoral bone.

Due to this knowledge, resurfacing implants has been developed to be used in young patients suffering from osteoarthritis. With this implant, only the damaged cartilage surfaces are replaced and the patient preserves the femoral head and neck. This should induced a more natural and physiological transfer of the load to the femoral bone and prevent osteolysis and aseptic loosening of the implant. Also, because of the larger head size, the range of motion should be better and a lower risk of dislocation. Furthermore, the metal-on-metal articulation is more wear resistant and polyethylene wear-particle formation should be reduced.

The aims of this thesis were 1) to investigate the survival of resurfacing implants compared to cementless total hip implants and to evaluate the causes for revision based on a literature search and meta-analysis, 2) in a randomized clinical trial to investigate the effect of two surgical techniques regarding the blood flow and metabolism in the femoral head during and after surgery, 3) to investigate the stability of the resurfacing implants at a five-year follow-up and 4) to investigate the soft tissues surrounding the hip implants, the bone mineral density and the clinical function of the resurfacing implants compared to hybrid, total hip implants in a five-year follow-up in a clinical randomized trial.

In study I literature search and a meta-analysis were performed. The results showed that the risk of revision was 1.86 times higher in resurfacing implants than in cementless total hip implants. The most common risks of revision in the resurfacing implants were femoral neck fracture and aseptic loosening of the implant.

In study II a comparison of two surgical techniques for insertion of resurfacing implants; the posterior surgical approach (standard approach in Denmark) and the antero-lateral surgical approach. Thirty-eight patients were included in the study. We measurement of the blood flow in the femoral head and neck was performed during surgery and the metabolism was assessed after surgery using microdialysis. The results from the Laser Doppler measurements showed no difference between the surgical techniques, whereas the results from the microdialysis showed a higher degree of ischemia when using the posterior approach.

In study III an analysis of the stability of the resurfacing implant was performed using radiostereometric analysis (RSA). We found, that the resurfacing implant was

stable at a five-year follow-up in a small group of patients. Second, we found that maker-based RSA as well as CAD (computer aided design) model-based RSA can be used to assess the stability of the implants. However, marker-based RSA was more precise whereas CAD model-based RSA was more clinically applicable. Finally, in a phantom study on resurfacing implants we found that marker-based RSA is the most precise method of analysis compared to CAD- and RE (reverse engineered) - model-based RSA when evaluating the stability. In study IV we included 19 resurfacing implants and 25 hybrid total hip implants and evaluated the patients at a five-year follow-up. MRI scan showed fluid-like collections surrounding the implants in 11 of 18 resurfacing hips compared to one of 23 total hip implants. DXA scans showed that the bone mineral density was preserved in the femoral neck in the resurfacing implants whereas in the total hip implants the DXA scan showed areas of decreased bone mineral density. Also, DXA scan showed that patients with resurfacing implants had less muscle atrophy compared to patients with total hip implants, whereas the range of motion was better in the total implants. We found no difference between the implants regarding the clinical results from evaluating pain and the clinical function of the hip.

2. Danish summary

Slidgigt er en invaliderende lidelse, der resulterer i smerter, bevægelses indskrænkning og nedsat funktionsniveau. Behandlingen ved fremskreden slidgigt i hoften er indsættelse af en hofteprotese og i Danmark indsættes årligt mere end 9000 hofteproteser. Prognosen for overlevelsen af en hofteprotese er god, hvis man er over 75 år, når man opereres første gang, hvorimod patienter under 50 år har en risiko på 20 % for at protesen skal skiftes indenfor 10 år. Dette skyldes primært at yngre patienter er mere aktive og derfor har et øget slid på deres hofteproteser.
Slid på hofteproteser resulterer i dannelse af slidpartikler. Disse består af de materialer protesen er laver af, oftest metal og polyethylen. Det er kendt at polyethylen partikler giver anledning til lokal knogle nedbrydning og senere protese løsning (aseptisk løsning), der ofte kræver at protesen skal skiftes. Derudover er det alment accepteret at udskiftning af en hofteprotese kan kompliceres af at man fjerner yderligere knoglevæv i lårbenskanalen, hvilket øger risikoen for at den nye protese ikke fikseres optimalt.
På baggrund af denne viden, har man i 1990´erne udviklet "resurfacing proteser" til yngre patienter med slidgigt i hoften. Ved denne protesetype udskifter man kun brusk-overfladen på lårbenshovedet samt hofteskålen. Dermed bevarer patienten lårbenshals og lårbenshoved, hvilket skulle give en mere naturlig vægtoverføring ned i lårbensknoglen og dermed forhindre knogleudtynding. Desuden skulle protesen give en bedre bevægelighed og mindre risiko for at protesen går af led på grund af det store ledhoved. Protesen er lavet at metal, i både hofteskåls og lårbens komponenten. Metal er meget slidstærkt og medfører ikke dannelse af polyethylen partikler.
Formålet med denne PhD var 1) at undersøge proteseoverlevelsen ved resurfacing proteser sammenlignet med ucementerede hofteproteser og samtidig ved en litteraturgennemgang at vurdere årsager til protese svigt ved resurfacing proteser, 2) at undersøge effekten af to kirurgiske adgange på blodgennemstrømning og metabolisme i lårbenshovedet i et klinisk randomiseret studie på resurfacing proteser, 3) at undersøge stabiliteten af resurfacing proteser ved en 5 års opfølgning og samtidig sammenligne forskellige metoder til vurdering af protesens stabilitet og 4) at sammenligne resurfacing proteser og hybrid proteser ved en 5 års opfølgning af et klinisk randomiseret studie med hensyn til bløddelsforandringer, knogle mineral indhold og kliniske resultater. I studie I udførte vi en litteraturgennemgang og en meta-analyse. Resultaterne viste at risikoen for en udskiftningsoperation var 1,86 gange større for en resurfacing protese sammenlignet med en konventionel ucementeret hofteprotese. De hyppigste årsager til udskiftning af proteserne var brud på lårbenshalsen og aseptisk løsning af protese komponenterne.
I studie II sammenlignede vi to kirurgiske adgange, der kan benyttes, når resurfacing proteser skal indsættes, henholdsvis den bagre adgang (standard i Danmark) og den forreste adgang. I alt blev 38 patienter inkluderet i studiet. Der blev udført måling af blodgennemstrømning med en laser Doppler under operationen og en kontinuerlig monitorering af metabolismen ved hjælp af mikrodialyse efter operationen. Resultaterne fra laser Doppler målingerne viste ingen forskel mellem de to kirurgiske teknikker, hvorimod resultaterne fra mikrodialysen viste en øget grad af iskæmi, når man anvendte den bageste adgang.

I studie III analyserede vi stabiliteten af resurfacing proteser med røntgen stereometri (RSA). I en gruppe på 19 patienter, fandt vi at protesen var stabil op til 5 år efter operationen. Desuden fandt vi, at man til vurderingen af stabiliteten, kan anvende såvel markør-baseret RSA samt CAD model-baseret RSA. Markør-baseret RSA mere præcis, hvorimod CAD model-baseret RSA var mere klinisk anvendelig. Et supplerende fantomstudie på protesen viste at markør-baseret RSA er den mest præcise metode, sammenlignet med såvel CAD- som RE- model- baserede RSA analyse metoder.
I studie IV indgik 19 resurfacing proteser og 25 hybrid hofte proteser. Resultaterne fra MR scanning af bløddelene omkring hofteproteserne viste en øget forekomst af væskeansamlinger omkring resurfacing proteserne sammenlignet med hybrid proteserne. DXA scanninger viste at knoglemineral indholdet i lårbenshalsen var bevaret ved resurfacing proteser, og at der var større områder i lårbensknoglen, hvor der var udtynding af knoglemineral indholdet ved hybrid-proteserne. DXA og MR viste at patienter med en resurfacing protese havde mindre atrofi af deres muskler omkring hofteleddet sammenlignet med patienter med en hybrid-protese. Bevægeligheden var imidlertid bedre hos patienterne med en hybrid-protese end hos patienter med en resurfacing protese. Der var ingen forskel på smerter og patient-tilfredshed mellem de to protese typer.

3. Introduction

The history of Hip Resurfacing Arthroplasty

End stage osteoarthritis of the hip is a disabling condition resulting in pain and impaired function. For more than half a century hip arthroplasty has been the gold standard in the treatment of end stage osteoarthritis. The evolution of the hip resurfacing arthroplasty is closely related to the developments and improvements in the history of the total hip arthroplasty.

The history of hip resurfacing arthroplasty (HRA) commenced early in the last century, when Mr. Smith-Petersen in 1923 performed the insertion of the mould arthroplasty. This prosthesis was made of glass and was only a replacement of the joint surfaces in an attempt to stimulate repair of the cartilage (159). Several implants broke due to poor strength of the bearing material but Smith-Petersen continued his search for new designs and materials over the following decades. This included testing of materials as pyrex-glass and celluloids but finally ended up with the use of Vitallium, a metal alloy consisting of cobalt, chromium and molybdenum (159).
The next step in the development of HRA was taken by Sir John Charnley in the late 1950s. His first attempts to produce a hip arthroplasty were also a surface replacement with bearing materials consisting of Teflon. Unfortunately this material resulted in accelerated wear rates and implant failure. Later, in 1962 his major breakthrough came with the invention of the low-friction Total Hip Arthroplasty (THA) with bearings consisting of metal-on-polyethylene (MOP) which became a great success due to pain relief and restored function in affected patients (38).
Several different designs of HRA were invented and this first generation of commercially-available HRA implants was introduced in the 1960s and 1970s. These implants consisted of cemented as well as cementless designs and used different bearing materials: metal alloys (cobalt-chromium-molybdenum), polyethylene, and ceramics (8;63;66;130;149;174;176). However, the HRA was almost abandoned entering the 1980s because of inferior implant survival (80). Despite the success of the Charnley implant, problems with aseptic loosening and failure due to wear particle-induced-osteolysis resulted in a renewed interest in metal-on-metal (MOM) bearings (89). Furthermore, a great number of THA with first-generation MOM articulating surfaces had been implanted throughout the 1960s and 1970s and acceptable long-term survival rates on the McKee-Farrar implant stimulated the MOM interest (14;86). This resulted in the production of the second-generation of MOM bearings with improved wear resistance and was also the reason for the revival of the HRA concept and the production of the second generation HRA (118;189;190).

Modern Hip Resurfacing Arthroplasty

Implants and design

Since the late 1990s, the second generation of HRA implants has been commercially available. The implants are made from the second-generation MOM bearing materials with improved metallurgy and tribology properties.
The concept of modern HRA is, in the majority of the available brands, a hybrid implant with a press-fit acetabular cup and a cemented femoral component (82). They differ only slightly in terms of geometry (radial clearance, wall thickness, and surface roughness) but exhibit differences in the composition and manufacturing of the bearing material. In the majority of the brands the bearing material consists of a MOM articulation made from a Cr-Co-Mo alloy (82;128). The use of MOM as the bearing material in hip arthroplasties differs greatly between countries. In Denmark only 2.3% of implants have MOM bearings whereas the corresponding number are 37% in the US, 12% in Australia respectively (3;4;104). One of the brands, the ReCap Femoral Resurfacing System from Biomet Inc. (IN, USA) was available on the market from 2003 and the first Danish implant was inserted in 2004 (see Figure 3.1).

Figure 3.1: The femoral component of the ReCap Total Hip Resurfacing implant from Biomet Inc. (IN, USA)

Patients

The implant has mainly been marketed for young and active patients due to several advantages: a lower risk of dislocation due to the greater diameter of the femoral head allowing a greater range of motion (ROM) after surgery, easier revision surgery due to bone stock conservation in the femoral neck and head, a more physiologic femoral loading resulting in less bone absorption through stress shielding, and a wear resistant MOM articulating surface allowing for a higher level of activity with reduced risk of osteolysis and aseptic loosening (109;122;155).
Today, the Danish indications of inserting a hip resurfacing implant is according to the Danish Hip Arthroplasty Registry as follows: primary osteoarthritis, age < 65 years in men and age < 55 years in woman (4). In Denmark, HRA has been used since 2004 and a total of 1098 implants have been inserted from 2004 to 2009 (4). In 2009, HRA accounted for 2.3% of all primary hip arthroplasties. Two thirds of the patients receiving a HRA were men and 44 % of the patients were aged between 40-49 years at surgery. Furthermore, primary osteoarthritis was the pre-operative diagnosis in 87% of the patients. In the United Kingdom and Australia the HRA implants accounted for 6% and 7.2% of all primary THA implants, respectively (3-5).

Implant survival

In the 1980s and 1990s problems with osteolysis and aseptic loosening of implants initiated by polyethylene wear-particles resulted in decreased survival rates of implants. This was a problem, especially in younger patients due to their high level of activity and hence the greater production of wear-particles (75;192). In clinical practice, younger patients were advised to reduce the level of activity to avoid dislocation of the implants and formation of wear-particles.According to the Danish Hip Arthroplasty Registry 2010, the overall ten-year survival of primary THA in patients older than 75 years at time of surgery is above 95%, whereas in patients younger than 50 years at the time of surgery, the survival is below 88% (4). In Denmark, the HRA 5-year survival rate was 94% in 2009 although this was based on a relatively small number of implants. In the United Kingdom and Australia the 5-year revision risk was 6.3% and 4.2%, respectively and this was almost a factor two higher than the revision risk in a cementless THA which were 2.3% and 3.3% respectively (3;5). Furthermore, the risk of revision among HRA patients was higher among women compared to men, in male patients older than 65 years compared to male patients younger than 65 years at time of surgery and patients with femoral component sizes smaller than 44 mm compared to component size 55mm (3). The reason for the elevated failure rate in woman is largely due to the fact that more women have smaller femoral heads and therefore have received smaller femoral components.

HRA and Risk Factors

HRA implants are associated with the same risk factors as THA. This includes infection, dislocation of the implant, component failure, and aseptic loosening of the components due to wear-particle-induced osteolysis. In general, follow-up on HRA implants have shown higher risk of revision among HRA compared to THA (158). The most frequently reported causes for failure are aseptic loosening of the components and femoral neck fracture (3). Lately, reports on soft tissue lesions possibly related to metal wear-debris have added to a growing concern for rare but harmful side-effects of HRA (70;76;111).

Complications Associated with Wear Particles

Wear Particles

MOM bearings are durable and resistant to wear. The annual wear rates have been estimated in retrieval analyses showing a mean wear of 25µm within the first year, decreasing to 5µm after three years, which is between ten to forty times less compared to the wear rate in MOP implants (53;157). Analysis of MOM wear particles found the mean size were considerably smaller (50-100nm) compared to the mean size of MOP wear particles that is known to induce aseptic loosening (0.5 - 1.0µm) (157). It is currently unknown if these nano-size wear particles have a different biological effect than larger size polyethylene particles. Even though the MOM bearing is more resistant to wear, the production of wear particles is greater

than in MOP implants. This is due to the fact that the size of the wear particles is smaller compared to the MOP particles (53).

Aseptic Loosening and Osteolysis

The survival of a joint implant is associated with the quality of the surrounding bone and a sufficient fixation of the implant into the bone tissue (114). The lasting (secondary) fixation can be obtained by either cement or by bone in-growth (press-fit implants). Aseptic loosening of a joint implant is defined as a mechanical loosening of the implant not related to infection. For decades, aseptic loosening has been the major cause of failure in hip implants. Today, aseptic loosening is still the most common cause for revision in hip implants and the risk is increased among young patients with cementless implants (4).

In the beginning the suspicion was directed towards fragments from the bone cement, bone cement-induced osteonecrosis, and the formation of a fibrous membrane between the bone and the implant. Later wear-particle accumulation was associated with aseptic loosening (74;89;139;192;193). DeLee and Charnley as well as Gruen have developed standardized grading systems to describe the anatomical propagation of osteolysis in both the acetabular and the femoral region, respectively (49;71).

The wear particles from polyethylene are strongly associated with a macrophage-mediated response resulting in osteolysis and predisposing to implant loosening (143). This is especially problematic among young and active patients, because they produce a high number of wear particles. Today, aseptic loosening is a common complication in HRA implants, accounting for 30% of all HRA failure registered in the Australian National Joint Registry 2010 (3). Still, more research is needed to clarify if the wear particles from MOM implants induce osteolysis through the same biological pathway as the MOP wear particles (185).

Soft Tissue Lesions

The revival of metal-on-metal (MOM) hip implants has been followed by a growing concern due to the increased release of metal wear particles compared with the amount of wear particle release from regular metal-on-polyethylene (MOP) implants (112). Studies have shown that wear particles from MOM implants are disseminated widespread in the organism and can be detected in the tissues surrounding the implant as well as in the blood, liver and kidney (87;111;112). Still large register studies have not been able to document any obvious link between serious systemically diseases and MOM wear particle release (188).

The possible adverse effects of MOM wear particles as metal sensitivity seen in dermatological reactions, bone necrosis, and implant loosening were described already in the 1970s (57;58). Within recent years a growing concern has re-emerged regarding these possible adverse effects of MOM wear particles as high metal ion levels were found in synovial fluid as well as peripheral blood. Periprosthetic soft-tissue masses (pseudo-tumors) in revised MOM implants have been described in several publications (70;70;111). The pseudotumors present as both solid and cystic lesions and are associated with muscle atrophy and tendon avulsions (76;148). Currently research is focused on the origin of this tissue reaction.

A histological diagnosis, ALVAL (aseptic lymphocyte vasculitis-associated lesion) has been established based on analysis of biopsies (45;126). So far, both a macrophage-induced cytokine response is found in MOP wear particle reactions, but furthermore a lymphocyte accumulation around vessel is present. This may be part of a delayed type IV hypersensitivity reaction and the immunological response to MOM wear particles may also lead to osteolysis (111). The different tissue reactions to MOM wear particles are not fully understood and follow-up on all patients with MOM implants is of great importance as well as further investigations to determine how the MOM wear particles affect the tissues.

Complications Associated with Bone Metabolism

Bone Metabolism

In general the term ”bone metabolism” is used as an equivalent for bone remodeling. Bone remodeling is defined as the constantly ongoing process in the bone tissue by resorption and ossification. Nevertheless, the definition of metabolism is the chemical reactions that occur within the cells, tissues, or an organism. This includes the processes of biosynthesis (anabolism) as well as the breakdown of organic materials, the energy delivering process in the cells (catabolism). In this thesis bone metabolism refers to the chemical reactions within the bone tissue during catabolism.
Metabolism as the energy delivering process in the bone tissue is depending on a sufficient supply of oxygen and nutrients (i.e. glucose) and a simultaneously removal of waste products (i.e. lactate). Important markers of metabolism are glucose, lactate, pyruvate and glycerol. Metabolism is sufficient if the energy production meets the tissue demands and impaired if the production does not meet the tissue demands. Insufficient metabolism can be caused by a decreased blood supply and perfusion of the tissue or an increased demand in the tissue in spite of normal blood supply and tissue perfusion.
During aerobic metabolism glucose and oxygen is metabolized into energy, water and carbon dioxide. However, if the metabolism is anaerobic, due to lack of oxygen, pyruvate - the degradation product from glucose metabolism - will not enter the citric acid cycle but will instead be converted into lactate by the lactate-dehydrogenase enzyme, and will then accumulate in the tissue. In case the tissue is deprived of energy to an extent leading to cell destruction, the breakdown of the cell membrane will cause increased levels of glycerol.

Blood Supply to the Femoral Head and Neck

Surgical Approaches in Hip Surgery

Several different surgical approaches have been developed for use in hip surgery (1). In Denmark as well as in the United Kingdom and Australia, the posterior surgical approach is used in the majority of the surgical interventions (1;3-5).
The posterior approach requires an opening of the posterior part of the hip joint capsule, where the median circumflex artery has its course in most humans (see Figure 3.2). The medial circumflex artery is thought to be the main blood supply to the femoral head and neck (18;65;90;151) with only minor contributions from the intraosseous blood flow and an anastomosis to the inferior circumflex artery (31;151;151). On the contrary, when performing a lateral or an antero-lateral approach (ad modum Watson), the posterior part of the hip joint capsule is left intact,

preserving the median circumflex arteries and thereby the blood flow to the femoral head and neck. Several studies have investigated the effect of the surgical approach on the blood flow in the femoral head and neck during surgery and found that the posterior approach results in a greater decrease in the blood flow than the antero-lateral approach (7;95;161;163).

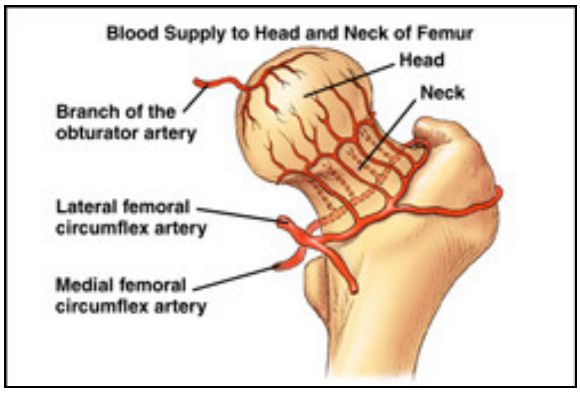


Figure 3.2: The blood supply to the femoral head and neck, with the medial circumflex artery localized on the posterior part of the capsule of the hip joint.

Ischemia and Hypoxia

Ischemia is defined as a standstill in the blood flow. Ischemia can be absolute or relative, and can be caused by either an arterial or a venous obstruction. Ischemia results in a reduction in the supply of oxygen as well as substrates (e.g. glucose). Hypoxia, which is an insufficient supply of oxygen, is a part of ischemia. Hypoxia can be caused by other reasons than standstill in the blood flow, such as an increased demand of oxygen in the tissue or a respiratory insufficiency. The consequence of hypoxia is an increase in the content of lactate (due to anaerobic metabolism) and an increase in the lactate/pyruvate (L/P) ratio, which represents the redox-potential of the tissue. An increase in the L/P ratio is equivalent to an increasing lack of oxygen in the tissue. Beside these changes due to hypoxia, the consequence of ischemia includes a decrease in the content of glucose which again will result in an elevated lactate/glucose ratio (L/G) ratio.

Avascular Osteonecrosis

Avascular necrosis (AVN) of the femoral head has been described in several studies (107;162) and can lead to implant failure and the need for revision surgery. The reason for AVN is not fully uncovered but a corner stone seems to be a disrupted or decreased blood supply, which may be initiated during surgery and may possibly depend on the choice of applied surgical approach. Several studies have shown (7;19;95) that the posterior surgical approach results in a 40-70% reduction in blood flow measured by Laser Doppler flowmetry.

Measurements of the cefuroxime concentration in soft tissue biopsies during hip surgery can be used as an indirect way to quantify perfusion (95) and have shown significantly lower concentrations when performing the posterior surgical approach. Furthermore studies using PET (positron emission tomography) scan after surgery have been used to evaluate the survival of the bone tissue in the femoral head and neck post-operatively by Ullmark et al. (177;178). They demonstrated that patients

developed areas of osteonecrosis in the femoral head one to five years after surgery. As the femoral component in the majority of second generation HRA implants is fixed to the host bone with a bone cement; the possible thermal effects of the cementation process is another possible explanation in the development of AVN. Beaulé et al. (22) have shown that the design of the HRA implant determines the thickness of the cement mantle and Little et al. (108) showed that a thick cement mantle results in higher temperatures as the cement cures. Yet the possible thermal effects from the cementation remains insufficiently investigated.

Femoral neck fracture

Femoral neck fracture (FNF) is the most common complication reported in HRA (3;9;115;164). Meticulous surgical technique and correct positioning of the implant seem to be important. Davis et al (46) showed that notching of the femoral neck during surgery would reduce the strength and increase the risk of femoral neck fracture and Vail et al. (182) demonstrated that notching of the superior part of the femoral neck resulted in a decrease in femoral neck strain by 21 %. Furthermore, a study by Richards et al. (144) demonstrated a significant increase in failure load for valgus-oriented components compared to neutral-positioned components.

Besides the importance of the correct surgical technique and implant positioning, AVN is another possible explanation in the development of the femoral neck fractures. Several studies have reported AVN in histological analysis of retrieved femoral head and necks after revision due to either femoral neck fracture or revision for other reasons (107;162).

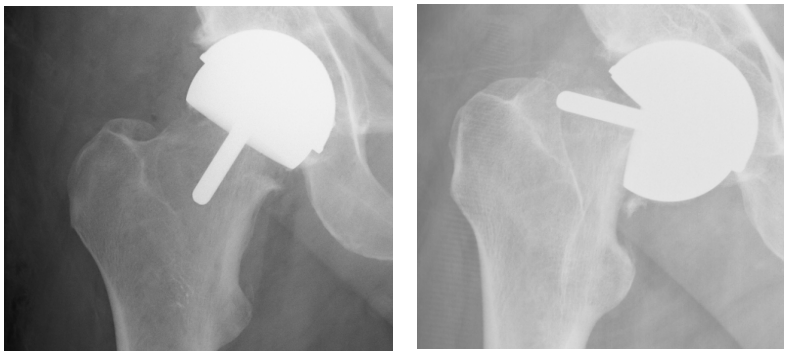


Figure 3.3: The ReCap Total Hip Resurfacing implant, inserted in the right hip of a patient. The left picture shows the post-operative radiograph with notching of the femoral neck and the right picture is a radiograph 2 months after surgery from the same patient, presenting with a femoral neck fracture.

Assessment of Bone Metabolism

Microdialysis

Microdialysis is a technique developed to monitor and quantify chemical substances in tissues. The initial steps were taken by Bito and Dawson in 1966 (27) who implanted a catheter in the ventricles of a dog brain and extracted cerebrospinal fluid for composition analysis. The technique was improved by Delgado (50) in the USA and by Urban Ungerstedt in Sweden who developed the method of microdialysis into the design and techniques used today (180). Today, the technique is minimally invasive and offers a possibility to monitor the chemical substances in tissues

continuously. The technique is based on a double lumen catheter with a semi-permeable membrane (see Figure 3.4). The catheter is connected to a pump and constantly flushed by an isotonic perfusion liquid (perfusate). The theory behind the technique is mimicking a human capillary with its permeability properties. The inlet tube of the catheter is constantly perfused at slow rate with the perfusate, allowing exchange of chemical substances and molecules bidirectional through the semi-permeable membrane. Due to the very slow perfusion rate of the perfusate a steady state will be obtained between the concentration of the substances in the interstitial tissue and the concentration of the substances in the perfusate. As the catheter is placed in the interstitial tissue it is only the concentrations of the substances in the extracellular space (and not the intracellular concentrations) which are monitored and only the free unbound substances can diffuse into the catheter. After collecting the perfusate, the analysis of the substrates can be performed immediately or stored for later analysis (see Figure 3.4, right).

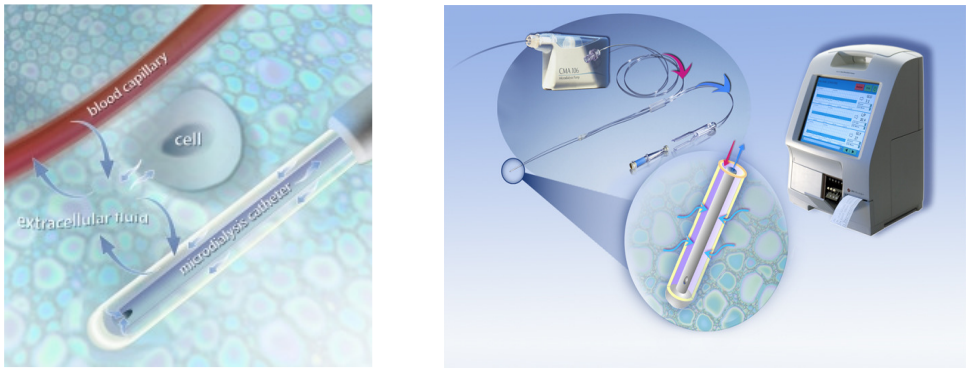


Figure 3.4: The microdialysis technique. The left picture shows a microdialysis catheter with exchange of substances across the catheter-membrane and the right picture shows a microdialysis pump and analyzer (right).

Originally, the scope for developing microdialysis was to investigate and quantify chemical substances in the brain (180). However, today the method is also used in a wide range of different organs and tissues in the clinic (26;94). Lately, experimental studies have been performed on muscle and bone tissue (29;30;141) and it has also been used to quantify the concentration of antibiotics in human bone tissue (169;170). Recovery is defined as the substances in the interstitial tissues diffusing into the microdialysis catheter, whereas delivery is defined as the substances in the perfusate inside the microdialysis catheter diffusing into the interstitial tissues. The ideal situation is a complete recovery of a substance, meaning that the concentration of the substance in the interstitial tissue equals the concentration of the substance in the perfusate inside the MD catheter. However, this is not always possible to obtain and in order to overcome this, the proportion of recovery - also called the relative recovery or the recovery rate (RR) – is often used. RR depends on several conditions such as perfusion rate of the perfusate and membrane characteristics such as membrane length and molecular weight cut-off level. Investigations have shown that a long membrane length and slow perfusion rate combined with optimal membrane pores is the ideal situation in order to obtain maximal recovery (179). However, recovery is of greatest importance when evaluating absolute values, whereas it is less important when evaluating ratios between substances or trends in substrate

concentrations over time regarding concentrations of metabolites obtained in comparable clinical settings.

Laser Doppler Flowmetry

Laser Doppler flowmetry (LDF) is a technique used to measure and quantify blood flow and perfusion in tissues. The principle in this technique was formulated by Johann Christian Doppler (1803-1853, Austria). In 1842 he wrote the paper "On the Colored Light of Double Stars and Some Other Heavenly Bodies" to the Royal Bohemian Society of Learning, formulating what has later become known as the Doppler Principle: a light beam hitting a static object will be scattered and returned with the same frequency, whereas a moving object hit by a light beam will be scattered and returned at a different frequency due to the Doppler-shift (6). For many years this theory was only used in the field of astronomy, until the late 1940s and 1950s , when the laser beam was invented by Charles Townes and Arthur Schawlow (6). The first results from LDF measurements on blood flow were published by Riva in 1972 (145) studying retinal vessels. In 1975, Stern developed the technique to measure the perfusion of a tissue as an alternative to blood flow measurements on a single vessel (166). Since then the LDF technique has been further developed into the commercial systems of Laser Doppler flowmeters available today (6).

When LDF are performed in tissue measuring the perfusion, a stable laser light is delivered to the tissue by an optic fiber and will be scattered by both moving and static objects. When the light beam is returned by static or moving objects the un-shifted light as well as the Doppler-shifted light are detected by one or several optic fibers and delivered to a photo-detector where the signals are amplified and processed and finally displayed as Flux units, which are arbitrary "perfusion units" . Flux units are calculated based on a calibration against a standard flux signal and are proportional to the product of the average speed of the blood cells and their concentration (6). Today LDF measurements have been used in a variety of tissues including bone tissue (7;19;29;168). The strength of this technique is to measure the change in the perfusion of the tissue, rather than the exact perfusion at a given time.

Radiologic Assessment of Orthopedic Implants

Radiostereometric Analysis

Radiostereometric analysis (RSA) is a highly accurate method developed to quantify micro motions between an implant and the host bone in a three-dimensional coordinate system. Long term survival of an orthopedic implant depends on implant stability; Kärrholm et al reported the clinical implication for migration of conventional cemented femoral stems with respect to the femoral bone and noted that that subsidence of more than 0.33mm combined with a total migration of more than 0.85mm was associated with increased risk of revision (93). The amount of subsidence at two years was an even better predictor of femoral stem loosening, and subsidence greater than 1 to 2 mm during the first two years was a positive prediction for revision in 50% of cases (93). Ryd et al assessed the prediction of early tibial component micro motion for prediction of the later revision risk, and described

two synergistic migration criteria that predict later tibial component aseptic loosening with a predictive power of 86% (147). Criteria #1 was continuously migrating implants above 0.2 mm/2 years. Criteria #2 was a mean migration above 2.7mm at 1 year and above 3.3 mm at 2 years or a 2-year migration that was 1SD larger than the group mean total migration (MTPM). The HRA is of different shape and has a different fixation and stress-loading than tibial components and stemmed femoral components. It is therefore unclear if the "migration-thresholds" suggested by Ryd et al for tibial components and by Kärrholm et al for cemented femoral stems also apply to HRA implants. RSA was formerly used to determine the micro motion of HRA implants after two or five years of follow-up and migration was overall below 0.2mm (16;85) without any early revisions. The "modern technique of radio stereometry" developed by Selvik in 1974 (152) is based on two simultaneous radiographs (stereo radiographs) of the patient and a calibration box. The use of two radiographs allows for the reconstruction of the position of the implant and the host bone in a three-dimensional coordinate system and calculation of micro motions between the two rigid bodies by use of mathematical formulas. The analysis can be performed as a marker-based method where tantalum markers are placed on the implant as well as in the host bone or as a model-based method where a reconstructed model of the implant is made by direct laser or optical scanning of the implant (reverse engineering, RE) or CAD models are used (92;152). Today, RSA is used to analysis the stability of different types orthopedic implants, however; the majority of studies are performed on knee and hip implants (60;61).

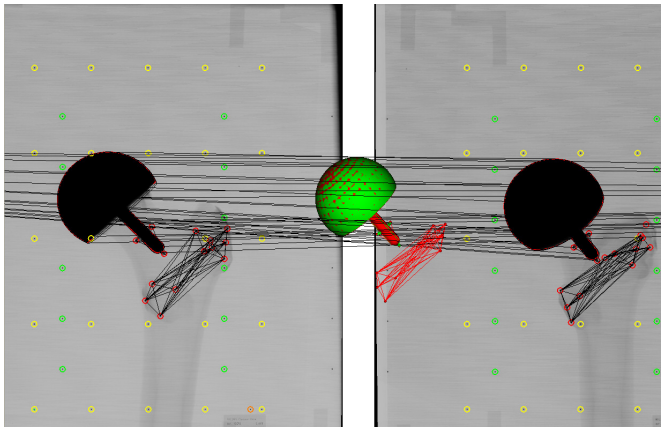


Figure 3.5: The figure shows results from a model-based analysis of an HRA implant (ReCap Total Hip Resurfacing, Biomet Inc.) using model-based Radiostereomteric Analysis (RSA).

Dual Energy X-ray Absorptiometry

Dual energy x-ray absorptiometry (DXA) is a standardized method to measure the bone mineral content also termed the bone mineral density (BMD). When inserting an implant it is of great importance to mimic the physiologic load on the bone in order to avoid stress shielding and bone resorption in accordance with Wolf's law. The first bone densitometer was developed in the 1960s by John R. Cameron (37). Since then the method has been further developed and is now widely used to evaluate the bone mineral density in assessment of osteoporosis and the BMD surrounding orthopedic implants.

The method is based on two x-ray beams with different energies. The energies are absorbed differently in bone or soft tissues (muscle and fat). When the energy

absorption from the soft tissues is subtracted, the absorption of the bone tissue can be determined and the BMD calculated. Equally, the density of muscle and fat can be determined. Scans of anatomical regions or the total body may be obtained in a short time (minutes).
Kroger et al. and Cohen et al. introduced DXA for use in orthopedic surgery with the first measurements of BMD around orthopedic implants and an assessment of the method reliability (39;42;102). Standardized grading systems have been developed to systematically evaluate the BMD around femoral and acetabular components (49;71). The seven Gruen zones used around the femoral component in THA are today being fitted to the femoral component of the HRA implants (Figure 3.5) (99) . Studies have shown an accelerated bone resorption within the first 3 months after insertion of a total hip arthroplasty, followed by a later increase in BMD (40;103). Today DXA is used to evaluate THA as well as HRA implants and it has been shown that precision in HRA implants is acceptable (41;73;127;137). Furthermore, it has been shown that the BMD increase is greater in HRA after two years follow-up compared to THA (78;99).

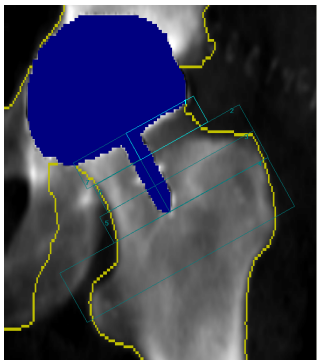


Figure 3.6: The figure shows results from a DXA scan and analysis of an HRA implant (ReCap Total Hip Resurfacing, Biomet Inc.).

Magnetic Resonance Imaging
Nuclear magnetic resonance imaging (MRI) was developed in the late 1970s. The technique is based on the manipulation of the nuclear magnetic dipole moments by means of an externally applied magnetic field and subsequent recording and analysis of the emitted radio-signals from the nuclei in response to these manipulations (59). The relaxation time is defined as the time it takes for the protons to emit their signal. The different tissues in the body exhibit different relaxations times which again is used in the imagining process to distinguish between the different tissues.
MRI is superior in the investigation of soft tissues in the human body due to the significant contrasts between different soft tissues in the body compared to x-ray or computed tomography. MRI was only recently introduced for assessment of peri-prosthetic tissues. In the beginning, problems arose due to the magnetization of the implant producing artifacts with void signals and distortion of the image (36). However, recent improvements in the MRI technique with improved scanners as well as the development of the MARS technique (metal artifact reduction sequences) have now made it possible to detect the soft tissues surrounding the implant as well as quantifying the bone tissues (36;140;191). MARS has been used to evaluate the soft tissue lesions detected in patients with MOM hip arthroplasties i.e. pseudotumors

(solid or cystic lesions), muscle atrophy, tendon rupture and lymph node abnormalities (76;148;195).

4. Aim and hypothesis of the thesis

The success of hip implants depend on the longevity of the implant combined with few implant related complications as well as pain relief, acceptable range of motion in the joint and patient satisfaction. HRA implants have re-emerged on the market within the last decade and the overall aim of this thesis was to evaluate HRA implants compared to THA implants in terms of implant failure rate and causes for failure, complications related to the implant, clinical performance, and patient satisfaction.

The specific aims of the 4 studies which this thesis is based were the following:

I. to assess the failures in hip resurfacing arhtroplasty compared to cementless total hip arthroplasty (the gold standard THA choice in Denmark anno 2011).
Hypothesis: HRA has higher failure rates compared to THA.

II. to investigate the effect of the surgical approach on the blood flow and the metabolism in the femoral head and neck in hip resurfacing arthroplasty.
Hypothesis: the posterior surgical approach results in increased ischemia in the femoral head and neck compared to the antero-lateral surgical approach.

III. to assess the precision of marker-based and two different model-based RSA methods with hip resurfacing arthroplasty in a phantom study. Second, to assess the clinical precision of marker-based and CAD model-based RSA based on double examinations and finally, to assess the stability of hip resurfacing arthroplasty five years after surgery.
Hypothesis: (1) marker-based RSA is more precise compared to CAD and RE model-based and marker-based RSA; (2) HRA is a stable implant five years after surgery.

IV. to evaluate the five-year results after hip resurfacing arthroplasty and conventional hybrid metal-on-polyethylene total hip arthroplasty (the gold standard THA choice in Denmark anno 2005) in a randomized study using MRI, DXA, radiological, and clinical evaluations.
Hypothesis: (1) HRA shows greater numbers of soft tissue lesions compared to THA; (2) HRA preserves the BMD in the femoral bone; (3) HRA has greater range of motion compared to THA.

5. Materials & methods

Design

I.

The study was a systematic review of the literature to assess the failure rates and determine the causes for failure in HRA implants. Furthermore, a meta-analysis was performed to compare the failure rates in HRA and THA (Level of evidence 1).

II.

The study was a randomized clinical trial comparing two surgical techniques when implanting a HRA to investigate the effect of the surgical approach on blood flow and the metabolism of the femoral head and neck (Level of evidence 1).

III.

The study was a combined phantom study and prospective clinical follow-up on HRA. The phantom study was designed to assess the precisions in marker-based and two different model-based radiostereometric analysis methods and the prospective five-year follow-up on HRA was performed to assess the implant stability using marker-based radiostereometric analysis and to validate the use of model-based radiostereometric analysis in a clinical setting (Level of evidence 2).

IV.

The study was a randomized clinical trial assessing the peri-arthroplasty soft tissue reactions, bone mineral density, osteolysis, and patient satisfaction in HRA compared to THA at a five-year follow-up (Level of evidence 1).

Patients

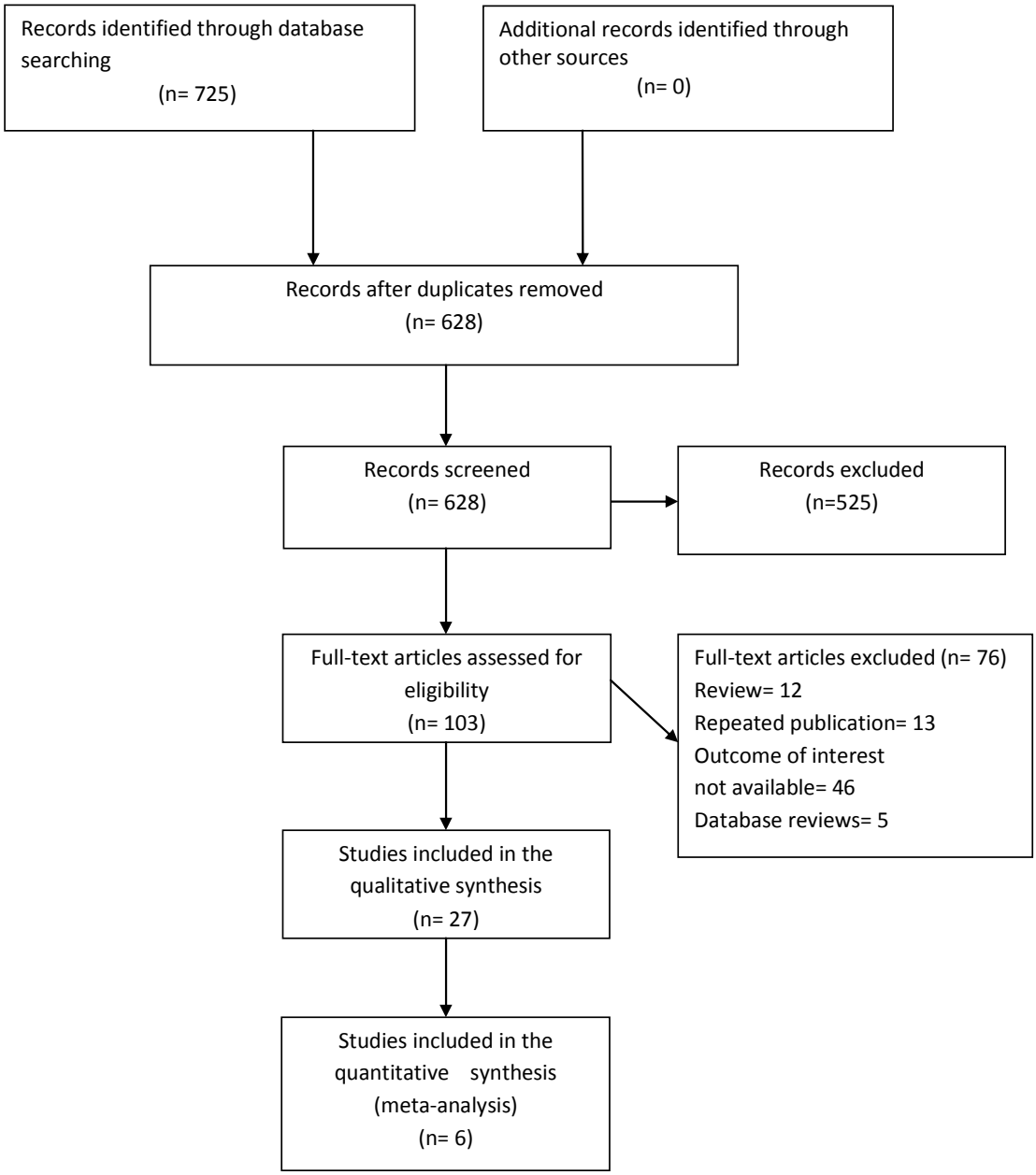
Study I

General description

The literature search resulted in 725 studies which were assessed for eligibility; this left a total of 27 studies to be included in the study, of which six studies were included in the meta-analysis. The total number of patients in the 27 studies was 10,544 (see the Prisma Flow diagram in Figure 5.1). Patient demographics are listed in Table 6.1. The studies were divided into two groups: Group 1 and Group 2. Group 1 represented observational studies on HRA. This group consisted of 21 studies, including 8,940 patients (9;15;23;44;47;67;81;83;88;96;98;113;115;117;124;129;133; 134;156;165;175). Group 2 represented 6 studies that compare HRA to THA; there were 5 observational studies and 1 randomized clinical trial (62;121;136;172;183;186). This group was divided into a HRA and a THA subgroup. Group 2 consisted of 1604 patients, with 857 patients in the HRA subgroup and 747 patients in the THA subgroup.

In Group 1, there was predominance of male patients in 20 of the 21 studies: this pattern was also seen in all of the studies in the HRA subgroup and in four out of six studies in the THA subgroup. The mean age in Group 1 ranged from 42 to 57 years. In the HRA subgroup, it ranged from 46 to 55 years and from 45 to 57 years in the THA subgroup. The mean body mass index (BMI) was not stated in all studies. The mean follow up time ranged from 0.5 to 10.9 years in Group 1, from 2.0 to 4.7 years in the HRA subgroup, and from 2.5 to 4.7 years in the THA subgroup.

Figure 5.1: Prisma flow diagram from study I.



Study II

In this study a total of 38 patients were included. The inclusion criteria of this study are listed in Table 5.1. All patients gave an informed consent based on information regarding project participation and were afterwards allocated to one of the two treatment modalities: 1) the posterior surgical approach (Post) or 2) the antero-lateral surgical approach (AntLat). The patients were bloc-randomized with five patients receiving the posterior approach and five patients receiving the antero-lateral approach in each bloc. Based on the sample size calculation in this study, 26 patients should be included with 13 patients each group. Since we expected that the microdialysis catheter could become displaced, which would exclude the patients from the study, we performed four bloc randomizations and a total of 38 patients were included. Of the 38 patients who were assigned to surgery, 16 patients were allocated to the Post group and 19 patients to the AntLat group.

Prior to surgery, all patients were found to be qualified for HRA after being evaluated with a pre-operative radiograph of the hip and a pre-operative DXA scan (osteoporosis scan) requiring a T-value> -1. Patient demographics of the two groups of patients are presented in Table 5.2. During surgery, three of the original 38 patients included in the study were excluded due to poor bone quality (two from the Post group and one from the AntLat group) leaving 35 patients to receive the allocated treatment. Furthermore, displacement of the microdialysis catheter in 11 patients (seven in the Post group and four in the AntLat group) resulted in nine patients in the Post group and 15 patients in the AntLat group entering the analysis (see consort flow-diagram in Figure 5.2).

Table 5.1: Inclusion criteria in study II

Inclusion criteria
Primary osteoarthritis or secondary osteoarthritis due to mild or moderate acetabular dysplasia
Acceptable bone mineral density on a pre-operative DXA scan (T-score > -1)
Age 30-60 years at the time of inclusion in the study
No vascular or neuromuscular disease in the operated leg
No fracture sequelae
No avascular necrosis of the femoral head
No wish to become pregnant
No alcohol abuse
No daily intake of non-steroid anti-inflammatory drugs (NSAID)
No daily intake of K-vitamin antagonists or loop diuretics

Figure 5.2: Consort 2010 flow diagram in study II

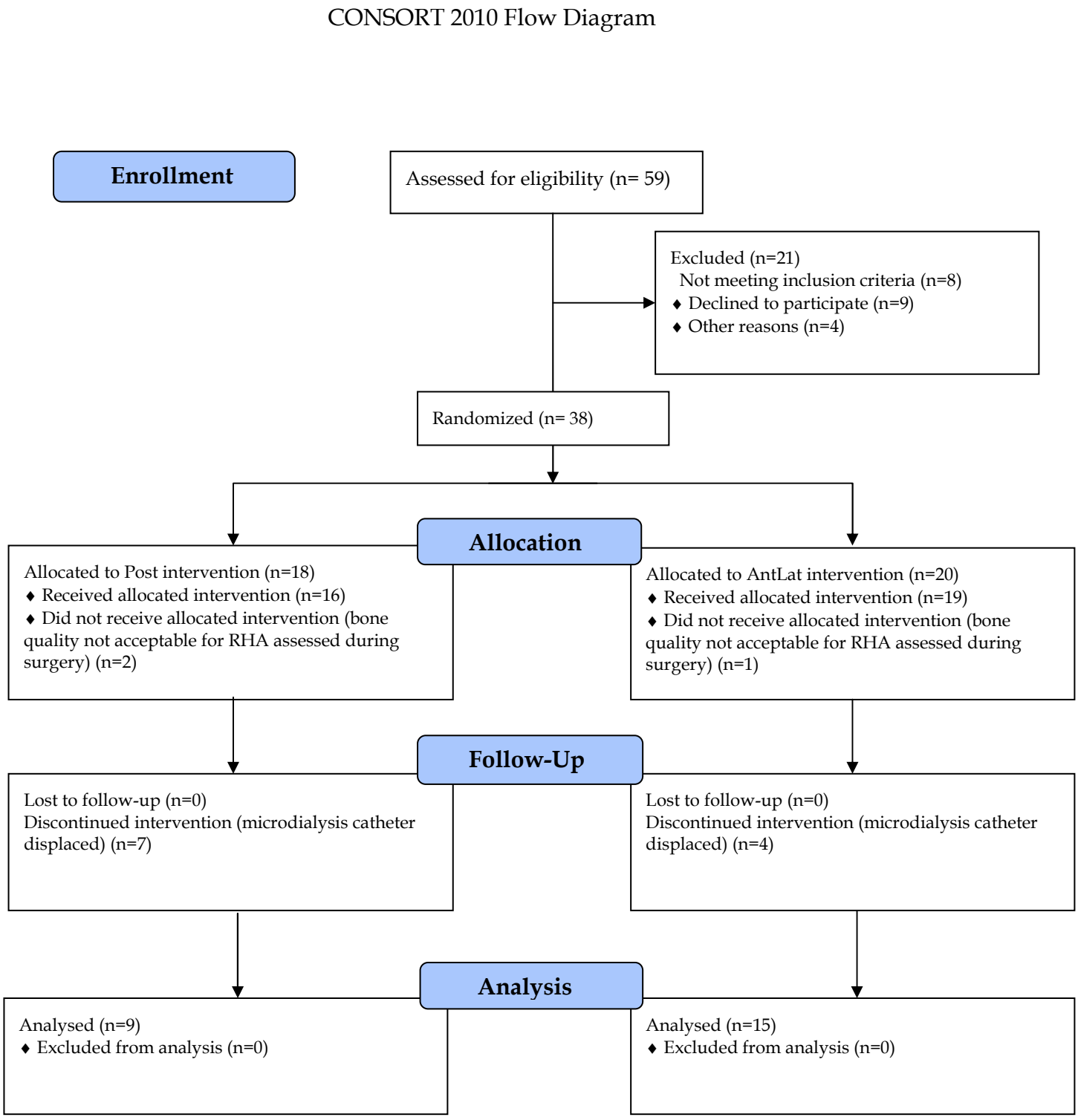


Table 5.2: Patient demographics in study II

Variables	Posterior approach	Antero-Lateral approach
Number of patients	9	15
Mean age (years)	45 (36-60)	53 (35-61)
Gender (female/male)	4:5	9:6
Mean BMI (kg/cm^2)	29 (23.7-34.4)	28 (22.4-37.9)
Mean blood loss during surgery (ml)	394 (200-900)	403 (150-800)
Mean femoral head size (mm)	48 (44-54)	48 (44-58)
Mean time (minutes)		
total surgery length	104 (75-120)	105 (85-130)
time from skin incision to implant cementation	77 (55-95)	71 (55-95)

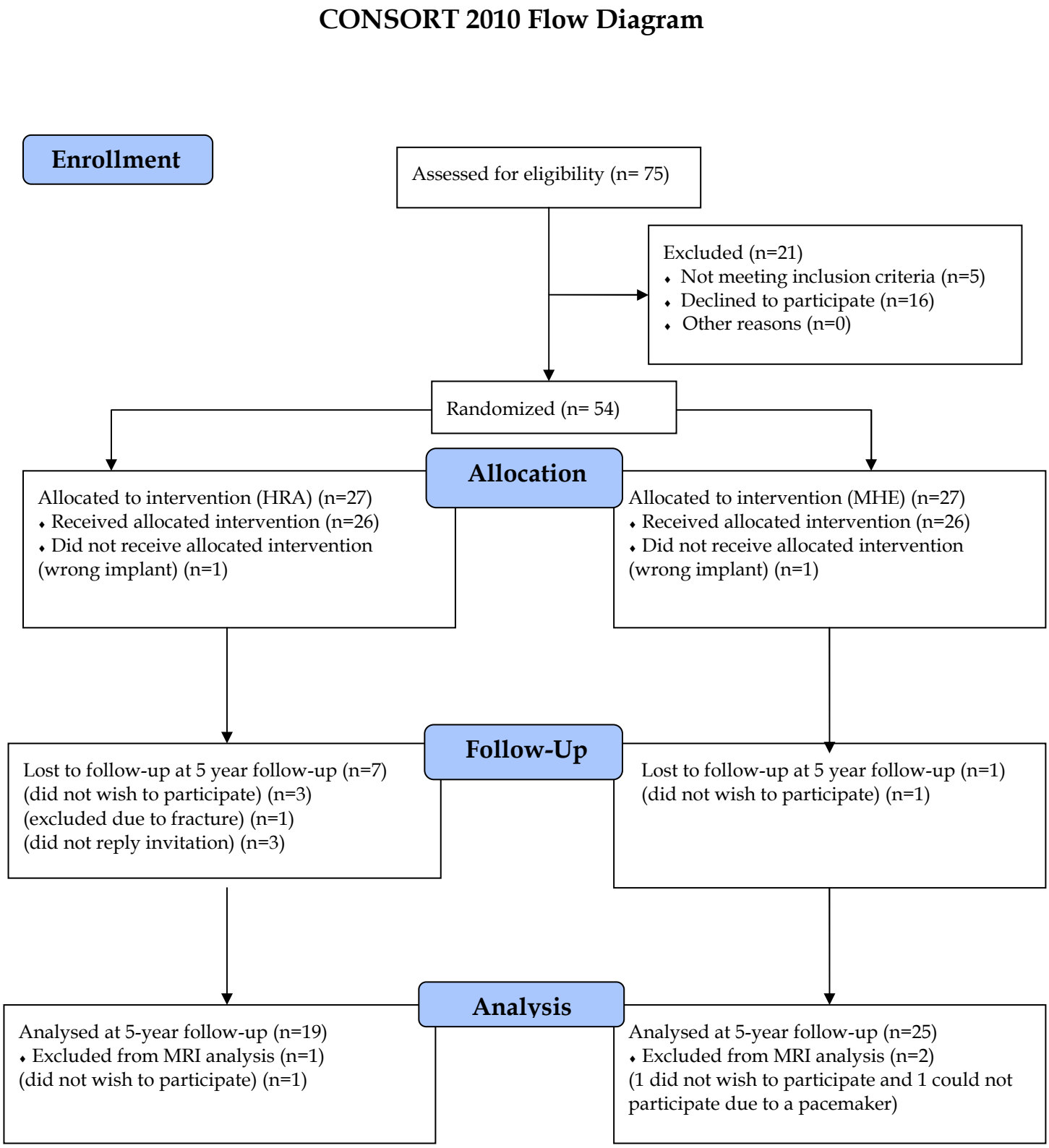
Study III & IV

In this study, fifty-four patients were included and the inclusion criteria were the following 1) primary osteoarthritis, 2) acceptable bone quality to allow the insertion of a HRA, 3) no regular intake of non-steroid anti-inflammatory drugs (NSAID), and 4) age between 50 and 65 years at surgery. After informed consent was obtained the patients were allocated to one of two treatment modalities: the MHE (Mallory-Head/Exeter total hip arthroplasty) group or the ReCap group. All patients were bloc-randomized with ten patients in each bloc (five ReCap and five MHE). Patient demographics at five-years after surgery are listed in Table 5.3. The results for up to two years after surgery from this trial have previously been published (16;138). Originally 54 patients were included in the study and 44 patients participated in the five-year follow-up (see consort flow-diagram in Figure 5.3).

Table 5.3. Patient demographics in study III & IV

Implant	ReCap	MHE
Number of patients=hips	19	25
Gender (M/F)	9/10	7/18
Mean age (years) at surgery	64 (56-70)	64 (57-70)
Mean BMI (kg/cm^2)	26 (19 -33)	27 (21- 32)
Mean femoral head size (mm)	48	28

Figure 5.3: Consort 2010 flow diagram in study IV



Implants

Study I
In the review of the literature we included studies which reported follow-up and failure rates on the second generation hybrid metal-on-metal (MOM) hip resurfacing arthroplasty, consisting of a cementless acetabular component and a cemented femoral component. In the meta-analysis we included studies comparing hybrid, MOM hip resurfacing implants to cementless, conventional total hip arthroplasties consisting of a cementless acetabular as well as femoral component. Different brands of implants were included as long as they fulfilled the above mentioned criteria.

In the 27 studies we included in the analysis, several different implants were used. The most frequently used HRA devices were the Birmingham Hip Resurfacing System (Smith & Nephew) and Conserve Plus (Wright Medical). Many of the resurfacing implants available today only differ slightly in terms of geometry, surface, and recommended surgical preparation. The implant types and manufactures are listed in Table 5.4.

Table 5.4: Implant brands in study I

Manufacturer	Implant
RHA	
Smith & Nephew	Birmingham Hip Resurfacing®
Wright Medical Technology	Conserve® Plus Total Hip Resurfacing System
Corin Medical Ltd.	McMinn Hip Resurafcing Arthroplasty
DePuy International Ltd.	ASR™ Articular Surface Replacement
Corin	Cormit 2000 Hip Resurfacing System
Zimmer™	Durom HR
THA	
DePuy International Ltd.	Summit®, Pinacle®, Marathon®, Ultamet®
Stryker Howmedica Osteonics™	Trident®, Accolade™
Wright Medical Technologies	Ancafit™ 28 mm ceramic on ceramic uncemented THA
Stryker	Osteonics ABC System
DePuy International Ltd.	G2®, Duraloc®, Pinnacle®, Marathon®
Zimmer™	CLS-Sporonto™, Allofit™ , Metasul™

Study II

All participants received the ReCap® Total Hip System (Biomet Inc., Warsaw, IN, USA). The implant was made of a chrome-cobalt alloy and consisted of a cementless acetabular cup coated with a Titanium Porous Plasma Spray Coating and a cemented femoral resurfacing component fixed to the bone with Simplex bone cement from Stryker®. Standard surgical equipment supplied by the manufacturer was used when inserting the implants.

Study III & IV

In the MHE group, patients received a hybrid implant consisting of a cemented Exeter stem (Stryker, Hopkinton, USA) and a cementless porous-coated Mallory-Head acetabular shell (Biomet Inc., Warsaw, Indiana, USA). The modular femoral heads were Alumina ceramic heads (Stryker) in 15 patients and Orthinox stainless steel heads (Stryker) in ten patients. The ReCap group received a ReCap Hip Resurfacing System (Biomet, Warsaw, Indiana, USA) consisting of a cemented cobalt chrome femoral component and a cementless titanium non-hydroxyapatite-coated closed-pore porous-coated acetabular component, with a cobalt chrome core fixed by press fit. In both groups the femoral component was fixed with either low viscosity Simplex P bone cement with Tobramycin (Stryker, Hopkinton, USA) or Palacos bone cement (Zimmer Inc.). Standard surgical equipment supplied by the manufacturer was used when inserting the implants.

Interventions

Literature search & Meta-analysis

Literature search and data extraction

First, a literature search was performed in the following electronic databases: Bibliotek.dk, SveMed+, CINAHL, Embase, PubMed, and the Cochrane Library. Furthermore the Danish Hip Arthroplasty Registry (DHR) and the Australian National Joint Replacement Registry (AOANJR) were searched. The following key words were used in the search with the Boolean operator "AND": resurfacing, hip, osteonecrosis, femoral head necrosis, failure, femoral neck fracture, osteoarthritis, treatment outcome, randomized clinical trial, follow-up, clinical trial, meta-analysis, practical guideline, replacement, and arthroplasty. To extract the relevant studies to be included in the analysis, we established a set of inclusion criteria.
The inclusion criteria are listed below:

- studies that compared HRA to THA or studies that evaluate HRA implants only
- randomized clinical trials and observational studies
- types of implants:
    - hybrid HRA consisting of a cementless acetabular component and a cemented femoral component
    - cementless THA regarding both the acetabular and the femoral component
- osteoarthritis as the primary diagnosis of treatment
- information of the number of failures in the study
- the English language.

Based on the literature search the identified records were assessed, all duplicates were removed, and the remaining records were screened based on the abstracts of the studies. Studies that did not fulfill the inclusion criteria were excluded and in the remaining records the full text articles were assessed for eligibility. Finally, the studies which fulfilled the inclusion criteria were included in the analysis and we extracted the following data if the information was available:

- age
- gender
- Body Mass Index (BMI)
- type of implant, intervention type (HRA or THA)
- surgical approach
- study outcome:
    - failure rate
    - causes of failure

We defined failure of an implant as revision surgery for any reason. The literature search was performed in June 2011.

Analysis of data
In all the studies included in the analysis, the total number of hips was registered as were the number of revisions and the different causes of failure leading to revision. Furthermore, the causes of failure were divided into five groups:

- aseptic loosening (either of the acetabular, femoral, or both components)
- femoral neck fracture
- avascular necrosis of the femoral head
- infection
- "other" causes which included:
    - pain
    - impingement
    - component failure
    - recurrent dislocation
    - femoral head collapse not associated to avascular necrosis
    - ALVAL (aseptic lymphocyte dominated vasculitis associated lesion)

Based on this, the risk of revision (failure rate) and the risk of the different causes for revision were calculated in each study. Furthermore we performed a meta-analysis to compare the failure rate in HRA implants compared to the failure rate in THA implants.

Surgical approaches

Study II
The patients were allocated to one of two different surgical techniques: the posterior approach or the antero-lateral approach. The posterior approach (ad modum Moore) was performed with a skin incision at the posterior part of the hip, the fibers of the gluteus maximus muscle were separated and the tendons from the external rotators were cut through. Finally the joint capsule was opened on the posterior part. On the contrary, when performing the antero-lateral approach (ad modum Watson), the skin incision was placed slightly more antero-lateral on the hip, the anterior third of the gluteus medius and minimus muscles insertion to the femoral bone were cut and the joint capsule was opened on the anterior part. All surgical procedures were performed by one of two senior surgeons at Aarhus University Hospital between November 2008 and December 2010.
In one patient, the surgery was performed after administering general anesthesia. The remaining patients received a spinal anesthesia combined with a supplementary sedation by intravenously administered propofol. These patients also received a transnasal supplement of oxygen (3L/min). All patients stayed in the hospital two to three days after surgery, and they all received similar post-operative rehabilitation which included mobilization within six hours after surgery and were allowed to put full weight on the affected hip.

Study III & IV

The ReCap implants and MHE implant were inserted by the posterior surgical approach. However, in the ReCap group partial detachment of gluteus maximus insertion at the femoral bone was performed since a greater incision was needed due to need for more internal rotation of the femur. All patients were operated on by two senior orthopedic surgeons at Silkeborg Regional Hospital (FML) and Aarhus University Hospital (TP) between January 2005 and August 2007. Three patients received administration of a general anesthesia whereas the remaining patients received a spinal anesthesia. All patients received the same post-operative rehabilitation and were allowed full weight bearing on the affected hip.

Laser Doppler flowmetry

Study II

Laser Doppler flowmetry is a validated method used to evaluate the blood flow and perfusion in a tissue of interest (24;131;173). Studies have shown that the blood flow in the femoral head is reduced between 40-70% if using the posterior surgical approach as compared to only 11% when using an antero-lateral approach (7;19). Laser Doppler flowmetry measures the blood flow in arbitrary units called Flux Units (FU) which based on several factors including the concentration and the speed of the red blood cells respectively. When using the laser Doppler flowmetry the blood flow in the femoral head and neck can be visualized as a pulse-synchronous sine curve.

In this study, laser Doppler flowmetry was performed in the femoral head and neck during surgery using a laser Doppler system from Moor Instruments Ltd., Axminster, UK. The laser Doppler was implanted in the needle probe model DP7HP-BS with a length of 120 mm and a diameter of 3 mm. The needle probe was a wide-separation needle with a maximum power of 2.5 mW, a wavelength of 785 nm, and the measurement area in front of the probe was 1 mm^3. The needle probe was calibrated against a standard reference of polystyrene microspheres provided by the manufacturer.

During surgery, the measurements were performed at the junction between the femoral head and neck in the upper quadrant of the femoral head. The exact location of the measurement was determined on the pre-operative radiograph, where we measured the distance (mm) from the lateral cortex to the junction of the femoral head and neck in the upper quadrant of the femoral neck (Figure 5.4). When inserting the ReCap implant, the femoral head was dislocated and the femoral head was visualized; a guide wire was inserted from the surface of the femoral head and under visual guidance pierced through the lateral cortex of the femur. Next the femoral head was relocated in the acetabulum and a canal was drilled in the bone over the guide wire, using a 3.5 mm drill.

After the canal in the bone had been prepared, the flow measurements were performed twice. The first measurement was performed shortly after the femoral head was relocated, and the second measurement was performed after the cementation of the femoral component was finished. At each measurement, ten seconds were recorded after a settlement of the sine curve was obtained. Blood

pressure and pulse rate were recorded simultaneously. Only data from recordings that showed a pulse synchronous sine curve was used in the statistical analysis. After the measurements were recorded, the difference between the first and second FU measurement was calculated as well as the relative change in blood flow for each patient, using the MoorSoftDRT4, Version 2.0 software.

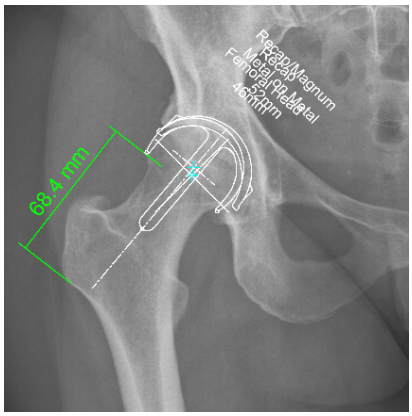


Figure 5.4: the figure shows a pre-operative radiograph used to perform the templating of an HRA implant. The length of the canal to be prepared to measure the blood flow at the junction between the femoral head and neck in the upper quadrant is measured and shown in green color.

Microdialysis

Study II

Microdialysis is a minimally invasive technique originally developed to measure human brain metabolism (146;179). In recent years microdialysis has been used in several experimental studies on porcine bone (30;169;170), whereas only one study has used microdialysis to measure human bone metabolism in an experimental study (29). These studies have shown that a complete interruption of the blood flow to the bone results in ischemia within two hours demonstrated by an increase of the lactate/pyruvate (L/P) ratio above 25.

The technique is based on a double-lumen, semi-permeable catheter which is placed in the bone tissue and perfused with an isotonic liquid. The theory of the technique is that the metabolites in the interstitial tissue of the bone will diffuse into the catheter, and, due to a slow flow rate of the perfusion liquid inside the catheter, a steady state will be established between the concentration of the metabolites in the interstitial fluid and the concentration of the metabolites in the dialysate inside the catheter. When the microdialysis technique is applied to the femoral bone in the post-operative period, the metabolism in the femoral head and neck can be quantified.

To estimate the metabolism in the femoral bone, we analyzed the following metabolic markers: glucose, lactate, pyruvate, and glycerol. We used a microdialysis catheter manufactured by CMA Microdialysis AB, Solna, Sweden, type CMA63 with a length of 60 mm, a diameter of 0.9 mm, a membrane-length of 10 mm, a membrane-diameter of 0.6 mm and a membrane cut-off level of 20.000 Daltons. After implantation of the HRA, the microdialysis catheter was placed under visual guidance in the upper quadrant of the femoral head at the junction between the

femoral head and neck. A 2 cm canal was drilled in the bone with a 2 mm drill at the same location where the flow measurements were performed. The catheter was tunneled from the skin surface, through the soft tissue to the femoral bone, and was fixed to the skin with a suture. A CMA 106 Microdialysis Syringe Pump was connected, and perfusion was performed continuously with an isotonic liquid (T1, CMA Microdialysis AB, Solna, Sweden). All the catheters were perfused with the same flow rate (0.3 µL/min) and the catheter was left in place until the patient was discharged between two to three days after surgery. The catheter had a golden tip at the end, which was visible on radiographs.
Within the first two days after surgery, all the patients were exposed to one plain radiograph, where the position of the microdialysis catheter was determined and registered. Samples were collected at intervals starting at 30 minutes and ending at three hours. The vials were collected and stored in a refrigerator at -20°C for a maximum of four weeks. Analysis of metabolite concentrations was performed, using the CMA600 analyzer, and the data was displayed using the Lab Pilot software (CMA Microdialysis AB, Solna, Sweden).

Radiostereometric Analysis

Study III

RSA set-up
In this study all stereo radiographs were obtained using a standard RSA setup consisting of two ceiling-fixed, synchronized roentgen tubes (Arco-Ceil/Medira; Santax Medico; Aarhus, Denmark) that were both positioned at a 20° angle with the vertical plane, and an unfocussed, uniplanar carbon calibration box (Box 24; Medis Specials, Leiden, The Netherlands). All stereo radiographs were digitized images (FCR Profect CS; Fujifilm, Vedbaek, Denmark) (1,760 x 2,140). All the analyses was performed using Model-based RSA (MBRSA) version 3.32 (Medis Specials, Leiden, The Netherlands) and all analyses were performed by two experienced RSA technicians. All ReCap implants had three tantalum markers (sized 1mm) attached to tip of three towers attached to the femoral component centralizer (Figure 5.5) and during surgery eight tantalum markers (sized 1mm) were inserted in the femoral bone corresponding to the greater and the lesser trochanter (Figure 5.6). For the model-based analysis a CAD model (2976 triangles) and a laser-scanned RE model (5000 triangles). The implant model (CAD or RE) had an inherent problem with y-rotation symmetry; however, the implant centralizer was not positioned in line with any of the three axes in the coordinate system (Figure 5.7).

Figure 5.5. The figure shows the femoral component of a ReCap Total hip Resurfacing with three towers attached to the centralizer (used to attach the Tantalum markers to the implant).

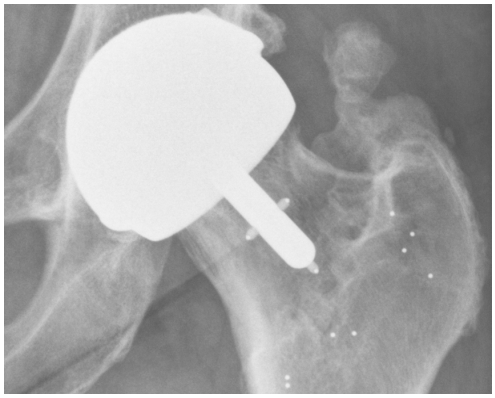


Figure 5.6. A radiograph showing a ReCap Total Hip Resurfacing implant with Tantalum amrkers placed in the greater and lesser trochanter as well on three towers attached to the centralizer of the femoral component.

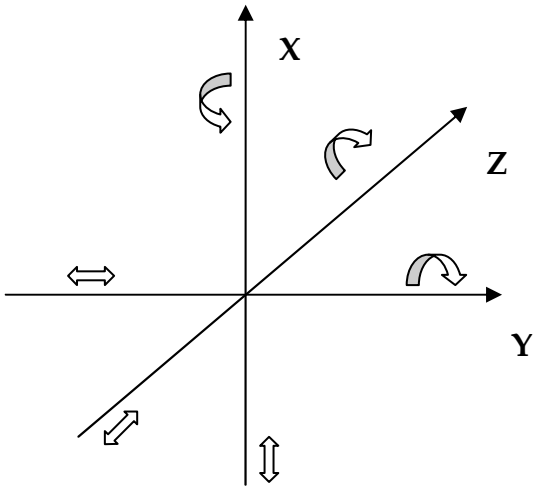


Figure 5.7. The coordinate system showing the direction of the translations (bidirectional arrows) and the rotations (curved arrows) along the x, y and z axis.

Phantom study
A phantom study was performed to determine the precision of the marker-based RSA compared to the CAD and RE model-based RSA, using a ReCap Hip Resurfacing femoral component sized 56 mm. The component was fixed to a synthetic femoral bone (Sawbones Europe AB, Malmo, Sweden), prepared equivalently to a standard surgical preparation and rigidly fixed. Furthermore tantalum markers were placed on the greater and lesser trochanter. Nine successive stereo radiographs were obtained with the phantom in nine clinically relevant positions. The stereo radiographs were analyzed using marker-based analysis as well as model-based analysis using a CAD model and a RE model. The radiographs were successively compared to the preceding picture (1-2, 2-3, 3-4 etc.). The mean condition number (implant marker dispersion) was 68 for the implant markers positioned at the centralizer, and the mean reference condition (bone marker dispersion) for the tantalum markers in the femoral bone was 16. The mean difference between model contour and implant contour (model pose estimation) was 0.1084mm in the RE model and 0.1037mm in the CAD model.

Double examination
A double examination was performed at the two-year follow-up in ten patients to assess the clinical precision of marker-based compared to CAD model-based RSA. In two of the ten patients, one or more markers were not visible, leaving eight patients for analysis. Between the double examinations the equipment was removed and the patients were repositioned. Optimally, the difference between the two measurements should be zero as the implant is not expected to migrate within the period of the examinations. The standard deviation (SD) of the mean between the double examinations represents the precision of the system and the limits of agreement (LOA, mean +/- SD*1.96) represents the expected clinical precision. The double examinations at the two-year follow-up were analyzed using both the marker-based RSA and the CAD model-based RSA.

Five-year follow-up
The stability of the ReCap implant at the five-year follow-up was determined by marker-based and CAD model-based RSA, respectively. The implant position relative to the host-bone (the femur) was determined in the RSA scenes from stereo radiographs that were obtained at each of five follow-ups (post-operatively, three months, one, two and five years after surgery). Migration at five years after surgery was calculated using the post-operative examination as the reference (184). All stereo radiographs were analyzed using both marker-based RSA and CAD model-based RSA.
In six patients, one or two implant-markers were occluded in either a single or in several stereo radiographic follow-ups (though not in the baseline image), whereas all these patients could be analyzed with CAD model-based RSA. However, to ensure a comparable patient-material for comparison of the CAD model-based and the marker-based RSA method, we excluded these six patients with occluded implant-markers in a single or in several radiographic follow-ups. Stereo radiographic analysis was completed with both methods at all follow-ups for 13 patients per follow-up. In the marker-based RSA the mean condition number was 63. The mean reference condition number was 18. The differences between the match of

the model contour and the implant contour (model pose estimation) was 0.1035 mm for CAD model-based RSA.

Magnetic Resonance Imaging

Study IV

In this study MRI was used to evaluate the soft tissues surrounding the hip implants. Earlier results from MRI scans of MOM implants were difficult to interpret since the metal articulations produced heavy artifact formation impeding the evaluation of the soft tissues around the implants. Recent studies (13;36) have shown that the soft tissues surrounding the MOM hip implants can be visualized with a minimum of artifact formation allowing the evaluation of the soft tissues. These soft tissue formations can be divided into cystic or solid lesions as well as it can be determinate weather they consist of muscle, fat, or water and an eventual capsular formation can be determined (13).

In our study all patients had an MRI scan of the pelvis and the proximal one third of both femurs in a private imaging center 0.35 Tesla scanner (Magnetom C, Siemens, Erlangen, Germany). The sequences were as follows: coronal T1 weighted (T1W) turbo spin-echo (TSE) echo time (TE)/repetition time (TR) = 19/583 milliseconds (ms); coronal STIR sequence, TE/TR/time of inversion (TI) = 86/5080/110 ms; axial T1W TSE, TE/TR = 544/9.4 ms; axial STIR sequence, TE/TR/TI = 79/7990/110 ms. Coronal and axial sequences had a section thickness of 8mm and 10mm respectively with intersection gaps of 0.9 mm and 1.2 mm. Field of view (FOV) was between 380 mm and the matrix 256x256. Images were assessed at the Aarhus University Hospital PACS work station by an experienced musculoskeletal radiologist (NE) in consensus with an orthopedic registrar (NDL).

We recorded the presence or the absence of intra- and extracapsular soft tissue abnormalities as well as bony abnormalities (148) were recorded in four sections of the joint replacement: above the cup, cup and head, neck and greater trochanter and distal to upper margin of the lesser trochanter. In each section the ventral, dorsal, medial or lateral location of a lesion was recorded. The size of each lesion was measured in three dimensions in millimeters. Contiguous lesions were measured and registered separately within each section and/or location.

Muscle atrophy was recorded on T1W axial images using the contralateral hip as the control (also with bilateral THR) for the three glutei, the obturator externus and internus muscles as well as the gemelli muscles. In addition the axial area of the right and left thigh was measured on the second section distal to the disappearance of the gluteus maximus muscle. The severity of muscle atrophy was graded 0-3 according to Bal and Lowe (17): 0=normal, 1= decrease in muscle mass not exceeding 30%, 2= 30%-70% fatty change and corresponding decrease in muscle mass, and 3=greater than 70% fatty change and muscle mass measuring less than 20% of the muscle mass in the contralateral hip. MR signal intensity (SI) of soft tissue, muscle and bone abnormalities was graded 0-2: 0=signal void, 1=signal equivalent to muscle and 2=hyper intense; on STIR sequence corresponding to water and on T1W corresponding to fat. Areas and lesions with high, grade 2 SI on both T1 and STIR sequences were considered metal artifacts.

Dual-energy X-ray Absorptiometry

Generally, the BMD in the femoral neck is conserved around the femoral component of HRA implants in all Gruen zones (78;99) whereas in THA implants there is a decrease in BMD most pronounced in Gruen zones 6 and 7 (43;106).

The patients participating in this study previously had DXA scans of the hip and spine and one- and two-year BMD data of the peri-prosthetic hip (Ortho Hip scan mode) were available from the primary study (and not previously published). At five years the hip scan was repeated and supplemented with a total body scan and an osteoporosis scan (spine and, if applicable, the non-prosthetic hip). A GE Lunar Prodigy Advance 2005 DXA scanner was used and the analysis was performed using the enCore 11.40 software. The bone, metal and soft-tissues were mapped automatically and metal was subtracted from the BMD measurements.

In the MHE group we analyzed BMD in the femoral bone applying the seven Gruen zones (see Figure 5.8) (71), and similarly we applied seven zones around the femoral neck in the ReCap group (see Figure 5.9). Once the Gruen zone template was locked to the baseline scan, and to maintain precision, the bone-edge and Gruen template from the baseline scan was copied to successive scans. Furthermore, in 30 patients (13 in Group MHE and 17 in Group ReCap) a double examination (double scan with a complete reposition of the patient between the examinations) was performed to determine the precision of the DXA scan and the Gruen zone measurements (69). For assessment of the mean muscle-mass and the mean fat-mass in the upper femoral region we used the total body scans. We created a custom circular region (CR) with a diameter of 13 cm, which was placed with the femoral head in the upper medial quadrant (see Figure 5.10) to quantify the local tissues surrounding the femoral head, neck, and trochanteric area. We further created a custom oblong region (OR) (see Figure 5.11), which included the tissues extending from the top of the femoral neck and including the proximal 2/3 of the femoral bone. 10 patients had a bilateral hip arthroplasty (second hip received after inclusion into the primary study).We used all the non-prosthetic contralateral hips (n=34) as a control group for comparison of the peri-prosthetic tissues (CR and OR).

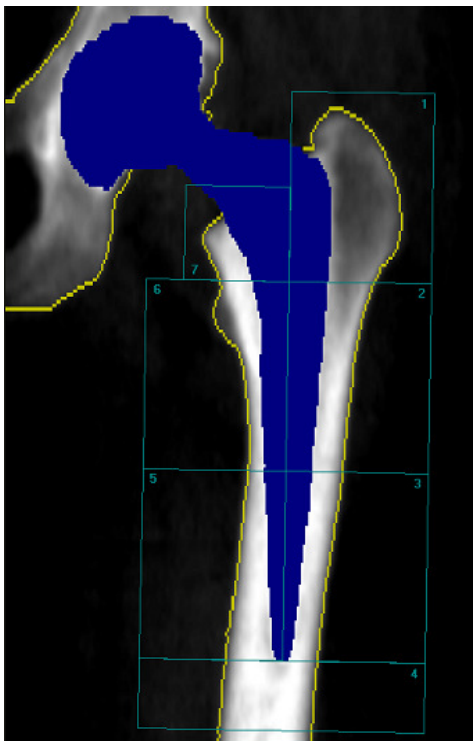


Figure 5.8: The figure shows the *Gruen zones 1-7 at the femoral bone around a MHE implant.*

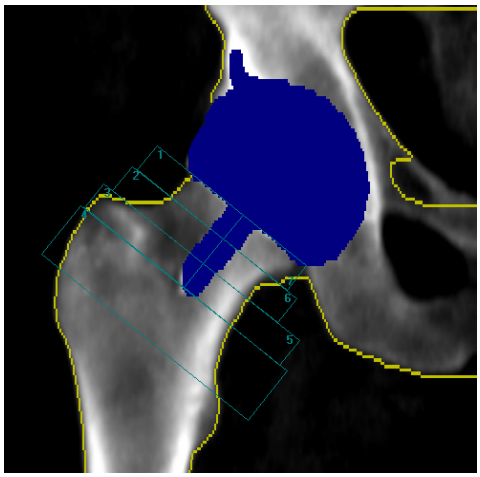


Figure 5.9: *The figure shows the Gruen zones 1-7 at the femoral neck around a ReCap Total Hip Resurfacing implant.*

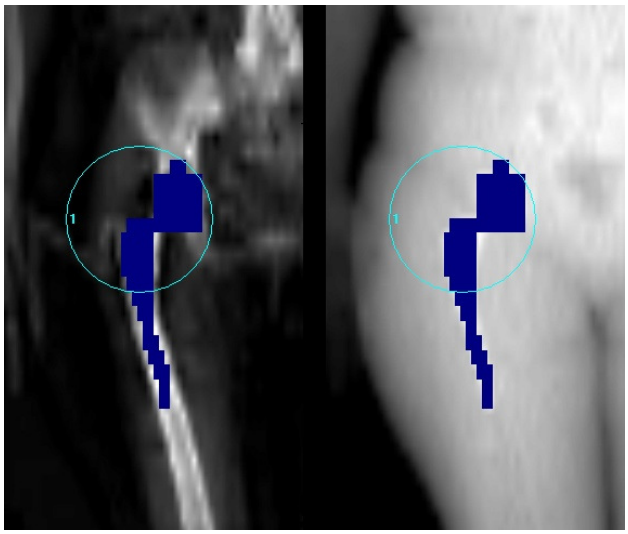


Figure 5.10. The figure shows the circular region of interest (CR) applied at the right femur of a MHE implant.

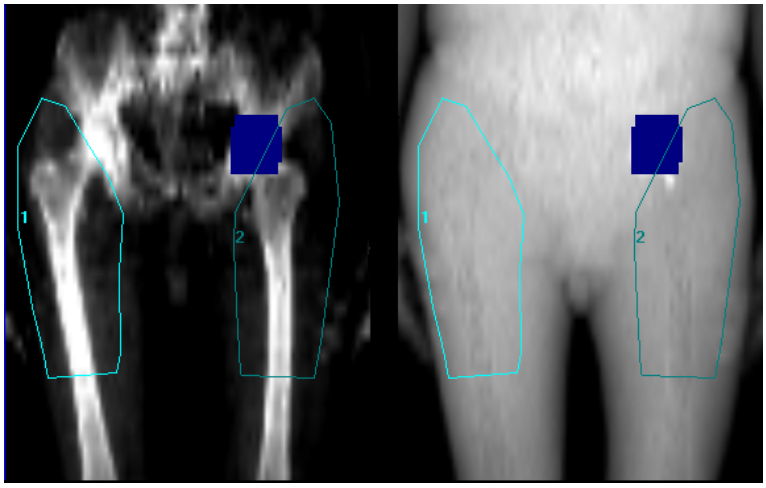


*Figure **5.11:** The figure shows the oblong region of interest (OR) applied at both femurs in a patient with a MHE implant.*

Radiographs

Study II

After surgery a plain AP (anterior-posterior) and lateral radiograph was performed to confirm the correct position of the inserted ReCap implant. Furthermore, these radiographs were used to confirm the position of the microdialysis catheter. The microdialysis catheter has a golden tip at the end of the catheter which is visible on radiographs. This way, the position and possible displacement of the catheter from the bone canal into the soft tissues surrounding the hip joint could be determined.

Study IV

Osteolysis was assessed on anterior-posterior and lateral five-year digital radiographs by a senior orthopedic surgeon (KS) in comparison with the post-operative hard-copy radiographs. Osteolysis was recorded corresponding to the Gruen zone 1-7 (71) in the femoral region and the DeLee zone 1-3 (49) in the acetabular region as the presence of either radiolucency lines greater than 1mm or expansile osteolysis (49;71). Furthermore the position of the femoral implant was determined as neutral, varus or valgus position. Heterotopic ossifications were rated according to the Brooker classification (35). The acetabular cup inclination and cup anteversion angle were assessed with Hip Analysis Suite (HAS) Software (116). Normally, a full pelvic radiograph is needed to aligning the horizontal axis in the image to measure the cup angles. At five-years we only had standard AP and LA hip radiographs and therefore we extrapolated the horizontal line between the ischial tuberosities in the preoperative hard-copy pelvic radiograph to the five-year digitized AP hip radiograph.

Clinical examination and questionnaires

Study II

Patients were evaluated pre-operatively and three months after surgery. All patients receiving the allocated treatment (N= 35) were examined and fulfilled the questionnaires. Patients were evaluated by the Harris Hip Score (HHS) completed by an orthopedic surgeon: the Oxford Hip Score (OHS) and the Visual Analogue Scale (VAS) score were completed by the patient. HHS evaluates the level of activity in daily living as well as a clinical assessment of range of motion in the hip joint and leg length. The maximum score is 100 and scores from 90-100 are considered excellent. OHS evaluates the level of activity without any clinical assessment and the score ranges from 0-48 with 40-48 categorized as normal joint function. Finally VAS was used to assess the level of pain associated with the prosthetic hip during daily living (average of the last four weeks). VAS ranges from 0 to 10, with 10 being the worst imaginable pain and 0 corresponding to no pain.

Study III & IV

All participants (n=44) were evaluated by the Harris Hip Score (HHS) completed by the surgeon, the Oxford Hip Score (OHS) as completed by the patient, and the Visual Analogue Scale (VAS) score.

Sample size

Study I
No sample size calculation was required in the review and meta-analysis.

Study II
The sample size was calculated using data from the laser Doppler flowmetry as well as the microdialysis. The power was set at 0.90, and the significance level was (α)=0.05. The laser Doppler flowmetry was estimated to have a minimal relevant difference (δ) of a 50% reduction in FU and SD within each group (σ) to be 30% change in FU (20). As for the microdialysis, δ was estimated to be 4 mmol/L and σ to be 1.5 mmol/L (29). This resulted in N=13 in each group for the Laser Doppler flowmetry and in N=8 in each group for the microdialysis. Due to a considerable risk of exclusion during surgery or displacement of the microdialysis catheter after surgery, we decided to include a total of 38 patients.

Study III
Originally, the sample size of the study was calculated based on the RSA and 23 patients were required in each group. A calculation of sample sizes in future studies based on the two RSA methods would require a minimum of 24 patients in each group. This calculation is based on a power of 0.90, σ=0.05 and mean TT marker-based =0.6 (SD=0.37) and mean TT CAD model-based= 1.20 (SD=0.82). Purely on marker-based the same calculation would require 23 patients in each group: thus CAD model-based RSA requires only a few more patients with the CAD model when assessing migration by the total translation.

Study IV
Based on the primary outcome in this study, soft-tissue lesions, we retrospectively calculated the sample size needed to reach a power of 95% based on the ratios we found regarding the fluid-like collections in the ReCap group and the MHE group, respectively. The significance level was set at 0.05, the power was set at 95% and the ratios of fluid-like collections in the two groups were 11/18 (0.6) and 1/23 (0.05), respectively. This resulted in a sample size of N= 19 in both groups. This sample size could be used in future studies investigating soft tissue lesion around hip joints by MRI.

Statistics

Study I

In Group 2, the studies comparing HRA to THA, we used the statistical program Comprehensive Meta Analysis (Version 2, Biostat, Inc.) to analyze and compare the failure rates in the HRA and the THA subgroup. The risk was calculated as a cumulated risk ratio (RR). The heterogeneity of the studies was tested using the χ^2 test, the meta-analysis was performed using the random effect model and results are stated with 95% CI intervals.

Study II

The results of the microdialysis were compared three times after surgery: one to three hours after surgery, 20-26 hours after surgery, and 44-50 hours after surgery. For each patient the median concentration of glucose, lactate, pyruvate and glycerol was calculated at those defined times. Next, the mean concentrations of glucose, lactate, pyruvate and glycerol were calculated in the Post group and the Ant-Lat group at each of those three times. In the same way, the lactate/pyruvate ratio (L/P ratio) and the lactate/glucose ratio (L/G ratio) were calculated for the three time-intervals. The concentrations of glucose and lactate are stated in mmol/L, and the concentrations of pyruvate and glycerol are stated in µmol/L. Mean values are stated with the standard error of the mean (SEM) in parenthesis. The microdialysis data were analyzed using the ANOVA to test 1) if there were significant difference between the groups with respect to changes in concentrations and ratios over time. The glycerol concentration and the L/P and L/G ratio were analyzed using log scale data.

The laser Doppler flowmetry data failed the normality test (Shapiro-Wilk test) and was analyzed using the non-parametric Mann-Whitney U test.

Study III

We calculated the mean and the standard deviations of the mean (SD) for the translations and the rotations regarding all three axes (x, y, and z axis) as well as the total translations (TT) and the total rotations (TR) in the phantom study, in the double examinations, and in the data from the five-year clinical follow-up. The precision of the analysis method was compared between the marker-based and the CAD and RE model-based RSA in the phantom study. The clinical precision was determined in the double examinations using the Pearson's correlation, where the standard deviation of the differences (SD_{diff}) represents the precision of the analysis method. The limits of agreement (LOA) represent the 95% limits of agreement and when comparing two different analysis methods LOA represent the reference range for the differences between the methods. LOA is defined as the mean +/- 1.96* the standard deviation (SD) or the standard deviation of difference (SD_{diff}) when analyzing a single method of analysis or comparing two different methods of analysis, respectively. LOA was used when comparing marker-based and CAD model-based RSA in the clinical data at the five-year follow-up. The mean total translations and total rotations were calculated using Pythagoras theorem ($\sqrt{X^2+Y^2+Z^2}$) (51). Continuous variables were tested for normality using the Shapiro-Wilk test and were compared using the t-test or, if they did not pass normality, the non-parametric Mann-U-Whitney.

Study IV

The mean BMD was calculated for all seven Gruen zones in both groups as well as the relative change in BMD from baseline (post-operatively) to one, two, and five years after surgery in all seven Gruen zones. Also, the mean BMD at baseline (post-operatively) was compared to the mean BMD at one, two, and five years after surgery in all seven Gruen zones in both groups. The mean VAS, HHS, and OHS scores as well as the mean range of motion (ROM) were compared between the groups at the five-year follow-up. In CR and OR we calculated and compared the mean fat mass and the mean muscle mass in the groups. In 30 patients a precision measure for the BMD evaluation in the Gruen zones was obtained from the double DXA scans to calculate the coefficient of variation (CV%) determined as SD/mean*100%, where SD represents the standard deviation of the difference between two measurements, to evaluate the precision of Gruen zone evaluation (69). Likewise a double analysis of CR and OR was used to calculate the CV% as a measure of the intra-observer variability (precision) when applying the custom ROI-templates to the total body scan. Based on the MRI scans the axial area of the muscle volume for each femur and the difference between the operated and the non-operated leg was calculated. The difference was compared within both groups and between the two groups. The continuous variables were tested for normality using the Shapiro-Wilk test and were compared using the t-test if appropriate. If they did not pass normality we used the non-parametric Mann-U-Whitney test or the Wilcoxon signed rank test. Categorical data were tested using Fishers exact test.

A p-value ≤ 0.05 was considered statistically significant. In all studies statistical analysis was performed using STATA 11.0 (STATA Corp LP, College Station, Texas).

Ethical issues

Study I
No patients participated and due to this no approvals were obtained.

Study II
The study was approved by the Central Denmark Region Committees on Biomedical Research Ethics (study ID number: M-20070082; date: 29-08-2007) and the Danish Data Protection Agency (study ID number: 2007-41-1559; date: 05-12-2007). Furthermore, the study is registered in Clinical Trials (Clinical Trials study ID number 20070082) and was conducted in accordance with the Helsinki II Declaration.

Study III - IV
The five-year follow-up was approved by the Central Denmark Region Committees on Biomedical Research Ethics (study number: M-20110038; date: 24-02-2011) and registered with the Danish Data Protection Agency (study number: 2007-58-0010; date: 30-03-201). Furthermore, the study was registered in Clinical Trials (study number: NCT 00116948; date: 30-06-2005) and was conducted in accordance with the Helsinki II Declaration.

6. Results

Study I

Failure rate

The failure rates in Group 1 ranged from 0.2% to 7.0%. In Group 2, the failure rates in the HRA subgroup ranged from 1.2% to 7.1% and in the THA subgroup from 0% to 4.3% see Table 6.1. In three of six studies, the failure rate in the HRA subgroup was larger compared to the failure in the THA subgroup (62;172;186). In one study, the failure rate was equal in the two subgroups (121), and in two studies the failure rates were larger in the THA subgroup (136;183). The meta-analysis that compared the failure rate in the HRA subgroup to the failure rate in the THA subgroup showed a risk ratio (RR) of 1.86 (1.00-3.46) using the random model analysis. This was statistically significant, with a p-value equal to 0.05 (see Figure 6.1).

Surgical approach

Among the 21 studies in Group 1, 16 reported the use of the posterior surgical approach in the majority of patients. In one study, they used the anterolateral approach (115), a trochanteric osteotomy approach in one study (23) and the surgical approach was not available in three studies (15;124;134). In Group 2, four of the six studies reported the use of the posterior surgical approach (62;136;183;186). One study used the anterolateral approach (121), and in one study, the surgical approach was not available (172).

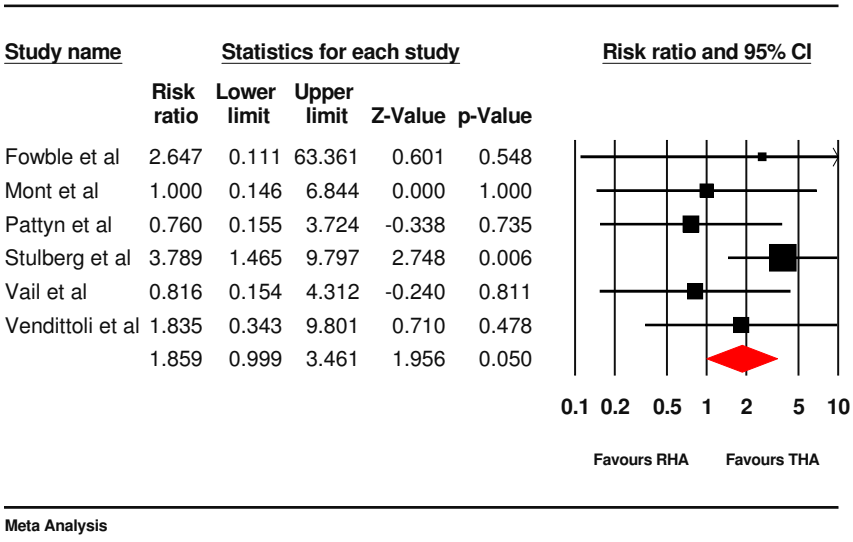


Figure 6.1. The figure shows a Forrest Plot showing the risk ratio (RR) in HRA compared to THA when comparing failure rates. The results are presented as risk ratio (RR). The red diamond represents the result from the meta-analysis, favoring THA implants.

Study	Implant	Year	N hips	N revisions	Failure rate (%)	Mean follow-up time (years)	Male/ Female	Mean age (years)	Mean BMI
GROUP 1									
Amstutz et al.	RHA	2008	1000	34	3.40	5.6 (1.1-11.0)	626/212	50 (14-78)	26.9 (17.5-46.4)
Aulakh et al.	RHA	2010	220	6	2.73	7.3 (2.2-9.8)* 7.5 (2.9-10) †	71/26* 73/22 †	43 (16-67)* 42 (16-65)†	NA
Beaulé et al.	RHA	2009	116	2	1.72	3.2 (1.0-7.0)	86/20	46.5 (19-62)	26.27 (18.24-38.82)
Daniel et al.	RHA	2004	446	1	0.22	3.3 (1.1-8.2)	302/82	48.3 (26-54)	26 (NA)
De Smet Koen et al.	RHA	2005	252	3	1.19	2.8 (2-5)	176/76	49.7 (16-75)	27.1 (18.8-47.9)
Giannini et al.	RHA	2011	142	5	3.52	6.1 (5.0-8.8)	70/52	50.3 (16-72)	NA
Heilpern et al.	RHA	2008	110	4	3.64	5.9 (5.0-7.8)	57/41	54.4 (35-75)	NA
Hing et al.	RHA	2007	230	2	0.87	5 (4-6)	140/72	52.1 (18-82)	27.02 (16.2-45.3)
Jameson et al.	RHA	2010	214	12	5.61	3.6 (2.5-4.75)	114/78	56 (28-74)	27 (19-30)
Khan et al.	RHA	2009	679	29	4.27	6 (5-8)	407/272	51 (15.8-87.9)	NA
Kim et al.	RHA	2008	200	14	7.00	2.6 (1.0-4.5)	156/44	48.5 (18-65)	NA
Madhu et al.	RHA	2011	117	8	6.84	7 (5.0-9.4)	59/42	54 (20-74)	NA
Marker et al.	RHA	2007	550	33	6.00	3.7 (0.6-6.3)	393/157	50 (18-79)	27.2 (17.7-48.2)
McBryde et al.	RHA	2010	2123	48	2.26	3.46 (0.03-10.9)	1324/799	55 (NA)	NA
Mont et al.	RHA	2007	724	15	2.07	2.8 (1.0-5.5)	160/454	50 815-81)	27.4 (18.2-48.2)
Nishii et al.	RHA	2007	50	2	4.00	5.6 (5-7)	21/24	51 (19-73)	23.1 (18.1-27.7) ‡ 23.4 (18.1-31.6) §
Ollivere et al.	RHA	2009	463	13	2.81	3.6 (0.5-7.5)	307/156	56 (20-70)	NA
O´Neill et al.	RHA	2009	250	8	3.20	2.0 (NA)	200/50	49.9 (NA)	28.3 (NA)
Siebel et al.	RHA	2006	300	8	2.67	0.5 (NA)	192/108	56.8 (18-76)	27.6 (19-41)
Steffen et al.	RHA	2008	610	23	3.77	4.2 (2.0-7.6)	316/216	51.8 (16.5-81.6)	NA
Treacy et al.	RHA	2011	144	10	6.94	10.9 (10.2-12.2)	107/37	52 (17-76)	NA
GROUP 2									
Fowble et al.	RHA	2009	50	1	2.00	3.2 (2.0-4.2)	31/19	46 (30-64)	27.3 (20.5-44.8)
	THA		44	0	0.00	2.5 (2.0-4.0)	18/26	55 (27-75)	31.3 (19.5-42.3)
Mont et al.	RHA	2009	54	2	3.70	3.3 (1-5)	36/18	55 (35-79)	29 (22-35)
	THA		54	2	3.70	3.3 (1-4.7)	36/18	55 (35-79)	29 (21-36)
Pattyn et al.	RHA	2008	250	3	1.20	ns (3-6)	165/85	49.54 (14-75)	27.1 (NA)
	THA		190	3	1.58	3 (NA)	112/78	44.95 (16-78)	25.5 (NA)
Stulberg et al.	RHA	2008	337	24	7.12	2.0 (NA)	228/109	50.1 (NA)	NA
	THA		266	5	1.88	2.0 (NA)	165/101	53.3 (NA)	NA
Vail et al.	RHA	2006	57	2	3.51	2.95 (2-4)	41/11	47 (22-64)	NA
	THA		93	4	4.30	2.0 (ns)	23/61	57 (17-92)	NA
Vendittoli et al.	RHA	2010	109	4	3.67	4.7 (3-6)	69/40	49.2 (23-64)	27.0 (17.6-44.9)
	THA		100	2	2.00	4.7 (2-6)	68/32	51.0 (24-65)	30.0 (17.4-49.1)

Table 6.1 (page 52): Patient demographics and failure rates in the studies included in study I; osteoarthritis (*), osteonecrosis (†), female patients (‡) and male patients (§) .

Causes of failure

The causes for failure in the two groups are listed in Table 6.2. In Group 1, the most frequently reported cause of failure was femoral neck fracture (35.4% of all failures in Group 1), which was reported in 18 of the 21 studies. The second most frequently reported cause of failure was aseptic loosening (31.8% of all failures in Group 1), which was seen in 17 of 21 studies, of which loosening of the acetabular component accounted for 56%. In the HRA subgroup, the most frequently reported cause of failure was aseptic loosening. This was reported in 3 of the 6 studies and accounted for 55.6% of the failures in the HRA subgroup, of which loosening of the femoral component accounted for 75%. The second most frequent cause was femoral neck fracture, which was reported in four of six studies and accounted for 30.6% of the failures.

In the THA subgroup, the most frequently reported cause of failure was aseptic loosening, which was reported in three of six studies, representing 25% of the failures and was equally distributed between the acetabular and the femoral component. Failure due to "other" causes was reported in three of six studies and accounted for 50% of all failures. The revision rate was larger among female patients in five studies and larger among male patients in one study (115;117;134;172;175).

Furthermore, four studies reported a significant correlation between elevated BMI and failure (98;115;134;156). Five studies found a significant correlation between small component size and failure (88;117;134;172;175). Kim et al.´s study reported a significantly larger revision rate among younger patients (98). Marker et al. found a significant association between cystic formations in the femoral head and failure (115). Siebel et al. and Marker et al. both reported a correlation between notching of the femoral neck and failure (115;156). Stulberg et al. found a low pre-operative Harris Hip Score to be associated with increased failure rate (172) . Finally, Kim et al found a correlation between the posterior surgical approach and failure (98).

Table 6.2 (page 54). Failure rates and causes for failure in study I. Aseptic loosening (asl), femoral neck fracture (nof), avascular necrosis (avn), infection (inf), "other" reasons (dislocation, component failure, ALVAL), acetabular component (AC) and femoral component (FEM).

Study	Implant	Year	N hips	N revisions	N asl	asl (AC-FEM-AC+FEM)	N nof	N avn	N inf	N "other"
GROUP 1										
Amstutz et al.	HRA	2008	1000	34	21	(1-20-0)	10	0	2	1
Aulakh et al.	HRA	2010	220	6	1	NA	3	0	1	1
Beaulé et al.	HRA	2009	116	2	2	(1-1-0)	0	0	0	0
Daniel et al.	HRA	2004	446	1	0	(0-0-0)	0	1	0	0
De Smet Koen et al.	HRA	2005	252	3	0	(0-0-0)	1	1	1	0
Giannini et al.	HRA	2011	142	5	1	(0-1-0)	3	1	0	0
Heilpern et al.	HRA	2008	110	4	2	(1-0-1)	1	1	0	0
Hing et al.	HRA	2007	230	2	1	(1-0-0)	0	0	0	1
Jameson et al.	HRA	2010	214	12	0	(0-0-0)	5	2	0	5
Khan et al.	HRA	2009	679	29	14	(9-5-0)	11	0	3	1
Kim et al.	HRA	2008	200	14	11	(10-1-0)	2	0	0	1
Madhu et al.	HRA	2011	117	8	2	(0-2-0)	5	0	1	0
Marker et al.	HRA	2007	550	33	10	(7-3-0)	14	0	4	5
McBryde et al.	HRA	2010	2123	48	9	(9-0-0)	13	6	4	16
Mont et al.	HRA	2007	724	15	4	(4-0-0)	6	0	0	5
Nishii et al.	HRA	2007	50	2	1	(1-0-0)	1	0	0	0
Ollivere et al.	HRA	2009	463	13	0	(0-0-0)	2	1	1	9
O´Neill et al.	HRA	2009	250	8	2	(2-0-0)	4	0	0	2
Siebel et al.	HRA	2005	300	8	3	(1-2-0)	5	0	0	0
Steffen et al.	HRA	2008	610	23	4	(3-1-0)	12	0	2	5
Treacy et al.	HRA	2011	144	10	1	(0-1-0)	1	3	3	2
TOTAL GROUP 1			**8940**	**280**	**89**	**(50-37-1)**	**99**	**16**	**22**	**54**
GROUP 2										
Fowble et al.	RHA	2009	50	1	0	(0-0-0)	0	1	0	0
	THA		44	0	0	(0-0-0)	0	0	0	0
Mont et al.	RHA	2009	54	2	1	(1-0-0)	1	0	0	0
	THA		54	2	1	(1-0-0)	0	0	1	0
Pattyn et al.	RHA	2008	250	3	0	(0-0-0)	1	1	1	0
	THA		190	3	0	(0-0-0)	0	0	1	2
Stulberg et al.	RHA	2008	337	24	15	(4-11-0)	8	0	0	1
	THA		266	5	1	(0-1-0)	0	0	1	3
Vail et al.	RHA	2006	57	2	0	(0-0-0)	1	0	1	0
	THA		93	4	2	(1-1-0)	0	0	0	2
Vendittoli et al.	RHA	2010	109	4	4	(0-4-0)	0	0	0	0
	THA		100	2	0	(0-0-0)	0	0	1	1
TOTAL HRA			**857**	**36**	**20**	**(5-15-0)**	**11**	**2**	**2**	**1**
TOTAL THA			**747**	**16**	**4**	**(2-2-0)**	**0**	**0**	**4**	**8**
TOTAL GROUP 2			**1604**	**52**	**24**	**(7-17-0)**	**11**	**2**	**6**	**9**

Study II

The microdialysis catheter was displaced in 11 of 35 patients (seven in the Post group and four in the AntLat group), leaving 24 patients for analysis (nine in the Post group and 15 in the AntLat group). We compared the mean concentrations of glucose, lactate, pyruvate, and glycerol at the three times indicated above and we found no significant different between the groups with respect to changes over time (p_{glu}=0.94, p_{lac}=0.99, p_{pyr}=0.91, p_{gly}=0.81, $p_{L/P}$ ratio=0.96 and $p_{L/G}$ ratio=0.99). Furthermore, we found significant changes over time regarding lactate (p<0.01) and glycerol (p<0.01) but no differences between the groups with respect to glucose (p=0.56), pyruvate (p=0.19), L/P ratio (p=0.73) and L/G ratio (p=0.16). Finally, the L/P ratio and L/G ratio was significantly higher in the Post group than the Ant-Lat group ($p_{L/P\ ratio}$=0.02, $p_{L/G}$=0.03) whereas we found no differences between glucose (p_{glu}=0.22), lactate (p_{lac}=0.07), glycerol (p_{gly}=0.07) and pyruvate (p_{pyr}=0.15). The mean concentrations of the four metabolites and the L/P and L/G ratio at the three time intervals are displayed in Figure 6.2 and 6.3, and the data is presented in Table 6.3. In the Post group, two out of nine patients showed no sign of circadian rhythm in the glucose concentrations and presented a low, flattened-off glucose curve and correspondingly high lactate curve (see Figure 6.4). This was only the case in only one of 15 patients in the AntLat group. The remaining patients all showed a circadian rhythm regarding the glucose concentration with an increase in glucose concentrations after meals and lower glucose concentrations during the night (see Figure 6.5).

Table 6.3. Result from the microdialysis with mean values of the metabolites and ratios. The standard error of the mean is stated in parenthesis.

Metabolite	Hours after surgery	Posterior approach	Antero-Lateral approach
Glucose (mmol/L)	1-3	1.87 (0.54)	2.46 (0.42)
	20-26	1.51 (0.69)	1.93 (0.32)
	44-50	1.83 (0.61)	2.43 (0.39)
Lactate (mmol/L)	1-3	8.37 (1.22)	6.28 (0.90)
	20-26	12.07 (0.75)	9.81 (1.03)
	44-50	10.47 (0.96)	8.27 (0.84)
Pyruvate (µmol/L)	1-3	231.11 (42.22)	152.34 (29.62)
	20-26	89.64 (14.39)	71.81 (9.33)
	44-50	82.25 (20.31)	63.61 (13.21)
Glycerol (µmol/L)	1-3	63.56 (16.95)	86.72 (12.89)
	20-26	91.63 (14.50)	104.43 (11.17)
	44-50	72.88 (14.16)	86.91 (9.56)
L/G ratio	1-3	240.01 (79.14)	132.86 (34.91)
	20-26	254.54 (18.00)	109.07 (19.43)
	44-50	208.53 (45.82)	128.04 (27.17)
L/P ratio	1-3	32.17 (18.01)	10.55 (5.02)
	20-26	27.98 (8.33)	13.38 (4.40)
	44-50	16.90 (6.55)	8.93 (3.73)

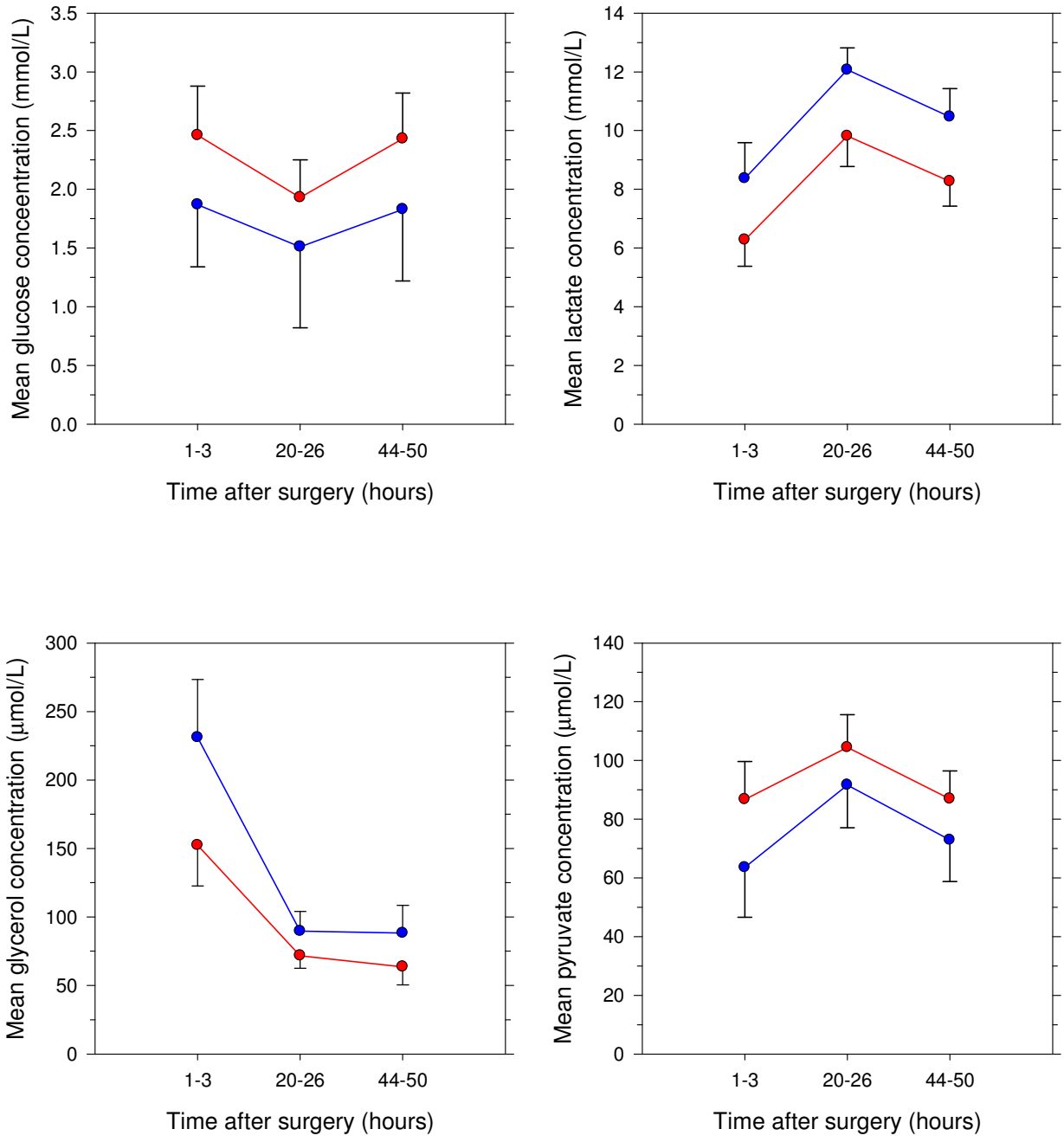
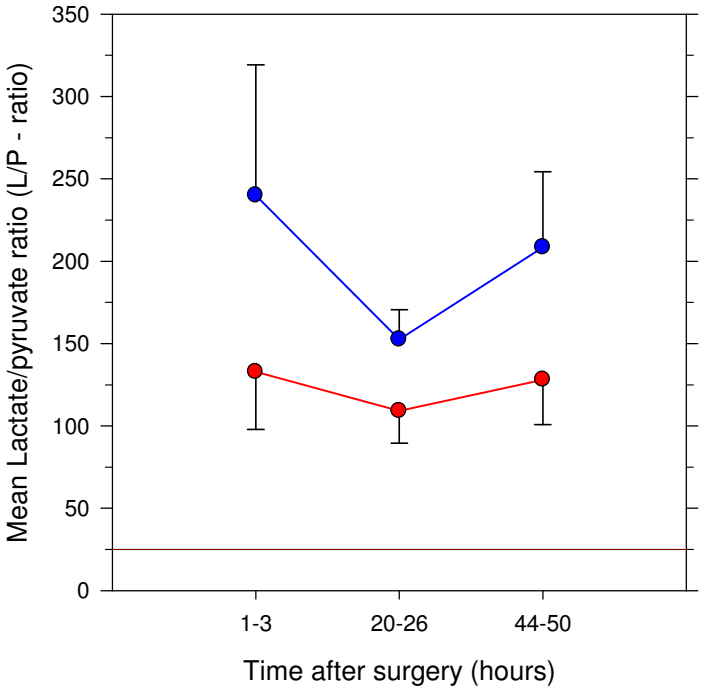


Figure 6.2. Results from the microdialysis. Mean concentrations of metabolites in the posterior surgical approach (blue curve) and the antero-lateral surgical approach (red curve), error bars represents the SEM. X-axis represents time after surgery (hours); glucose (top left), lactate (top right), glycerol (bottom left) and pyruvate (bottom right).



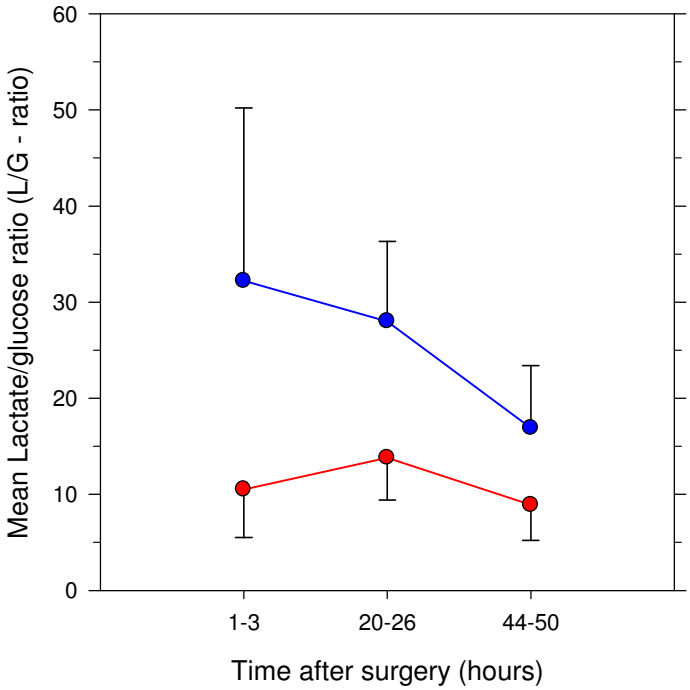


Figure 6.3. The mean L/P (top) and L/G (bottom) ratio in the posterior surgical approach (blue curve) and the antero-lateral surgical approach (red curve). Error bars represents the SEM. X-axis represents the time after surgery (hours). At the curve showing the L/P ratio, a horizontal line has been added, representing a L/P ratio of 25, which defines ischemia.

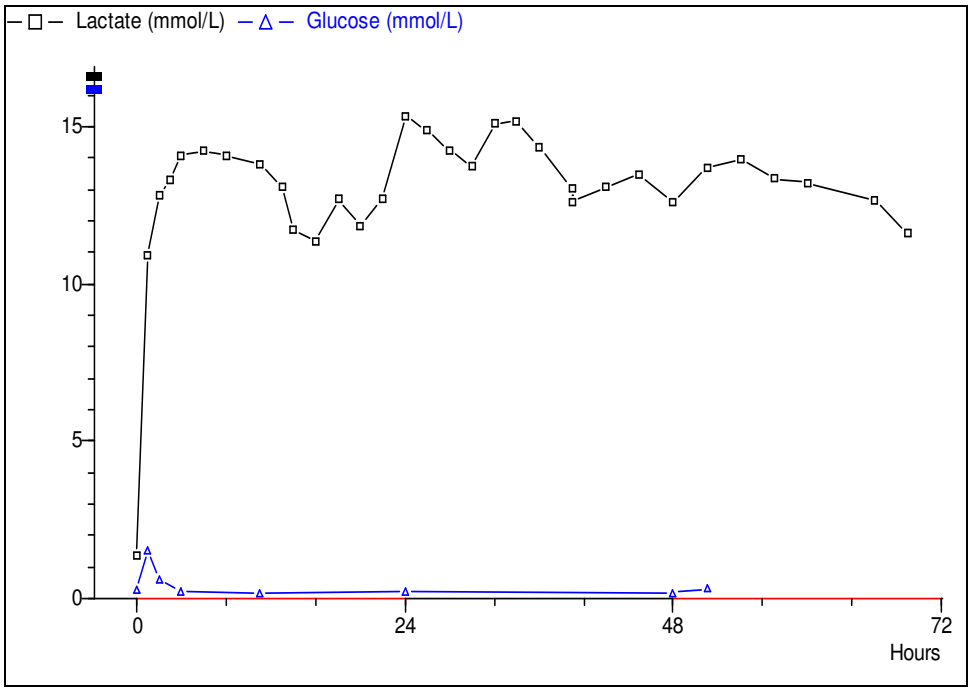


Figure 6.4. An example of microdialysis results from an absolute ischemic patient, with high lactate concentrations (black curve) and a flattended blue curve without circadian rhythm, representing the glucose concentration. The x-axis shows the time after surgery (hours).

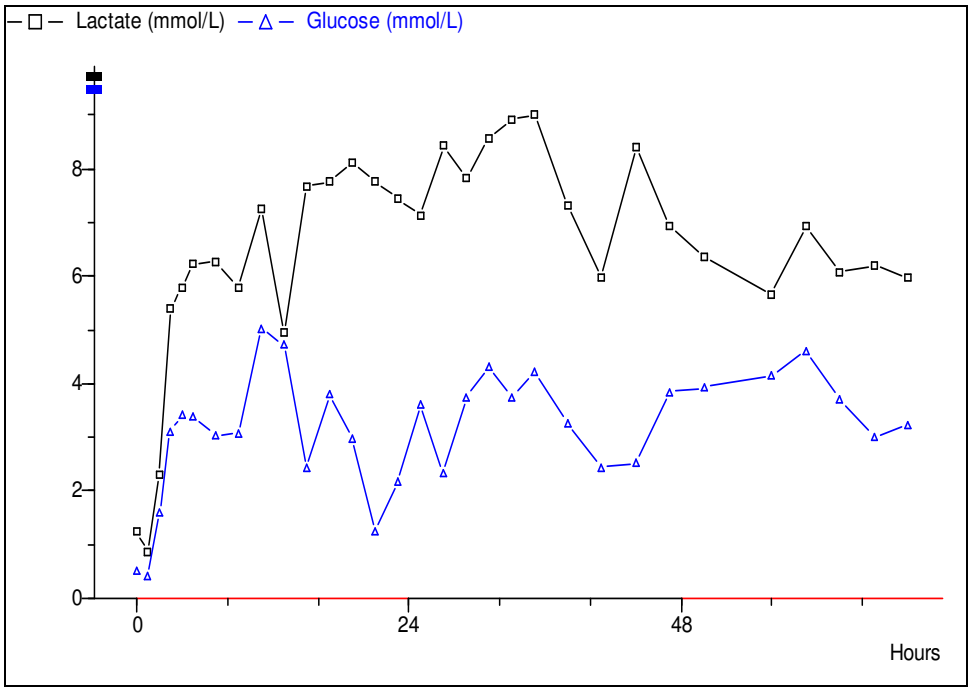


Figure 6.5. An example of results from a relative ischemic patient. The lactate concentration is increased (black curve). The glucose concentration (blue curve) shows a circadian rhythm. The x-axis represents the time after surgery (hours).

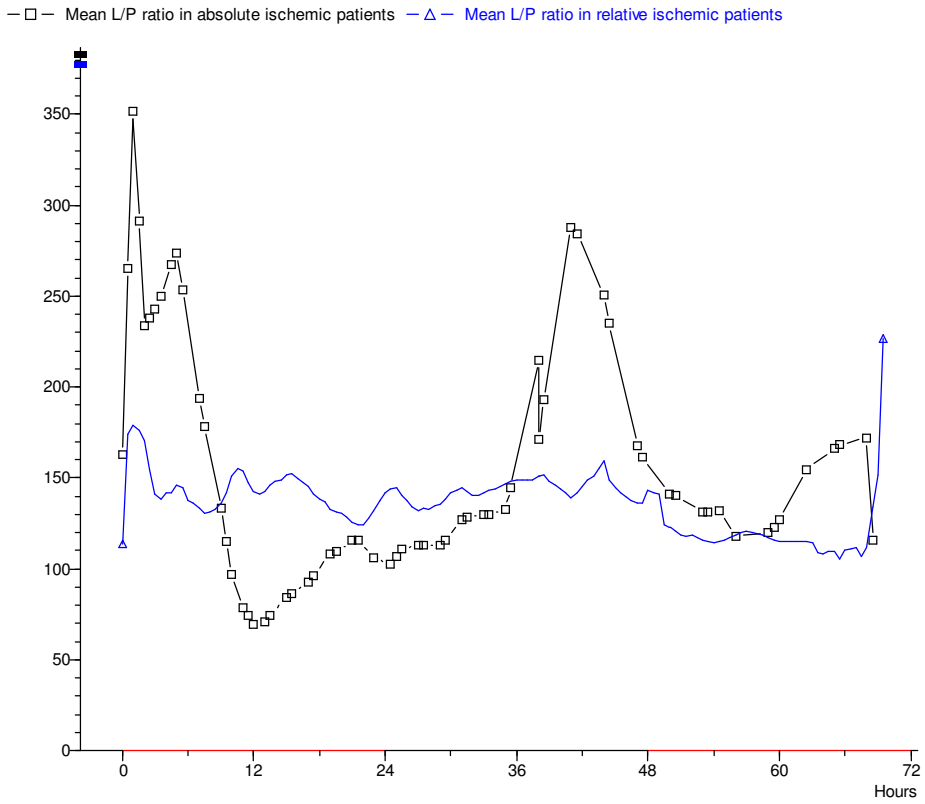


Figure 6.6. The mean L/P ratio in relative (blue curve) and absolute ischemic (black curve) patients. The x-axis represents hours after surgery; the y-axis represents the L/P ratio. The black curve represents the mean L/P ratio 3absolute ischemic patients and the blue curve represents the mean L/P ratio in 21 relative ischemic patients.

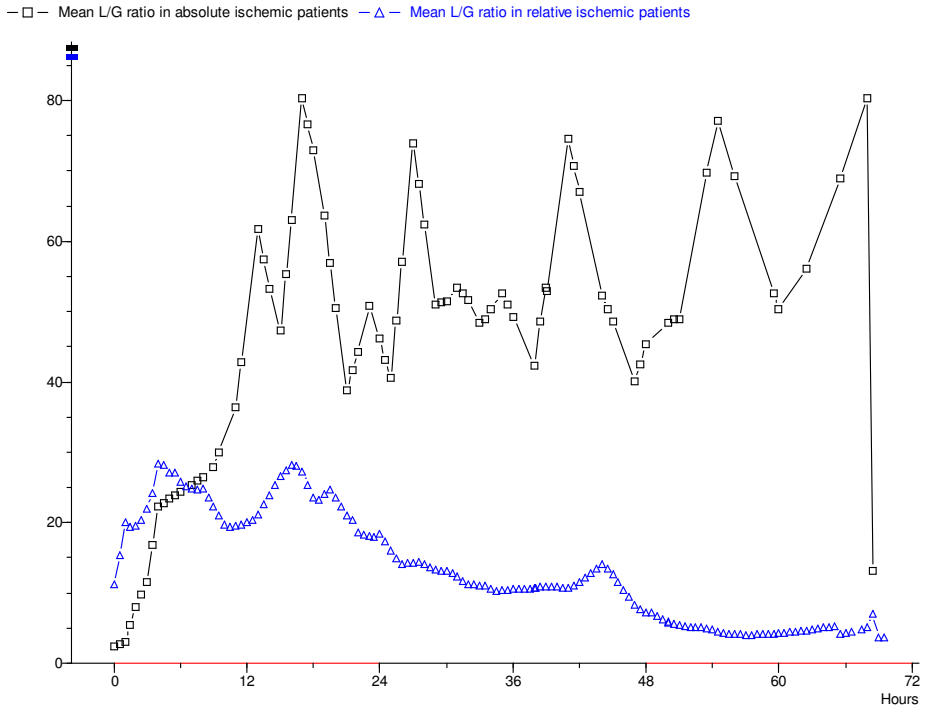


Figure 6.7. The mean L/G ratio in relative (blue curve) and absolute ischemic (black curve) patients. The x-axis represents hours after surgery; the y-axis represents the L/G ratio. The black curve represents the mean L/G ratio 3 absolute ischemic patients and the blue curve represents the mean L/G ratio in 21 relative ischemic patients.

Laser Doppler flowmetry was performed on 35 patients. Seven of the 35 recordings were excluded from the analysis due to lack of a pulse synchronous sine curve, leaving 11 in the Post group and 17 in the AntLat group. In the Post group, the mean reduction in FU was 38.5% (18.6), and in the AntLat group it was 43.8% (10.6). There was no difference between the two groups (p=0.74). In the Post group, eight of 11 patients showed a decrease in FU from the first to the second measurement, and three patients showed an increase in FU. In the AntLat group, 14 of 17 patients showed a decrease in FU and three patients had an increase in FU. The results are shown in Figure 6.8.
During surgery, none of the patients showed any significant changes in blood pressure, pulse rate or oxygen saturation measured peripherally. Furthermore, the temperature in the operating room, the total amount of bleeding during surgery and the length of time of surgery as well as the length of time from skin incision to cementation of the femoral component were equal in the two groups.

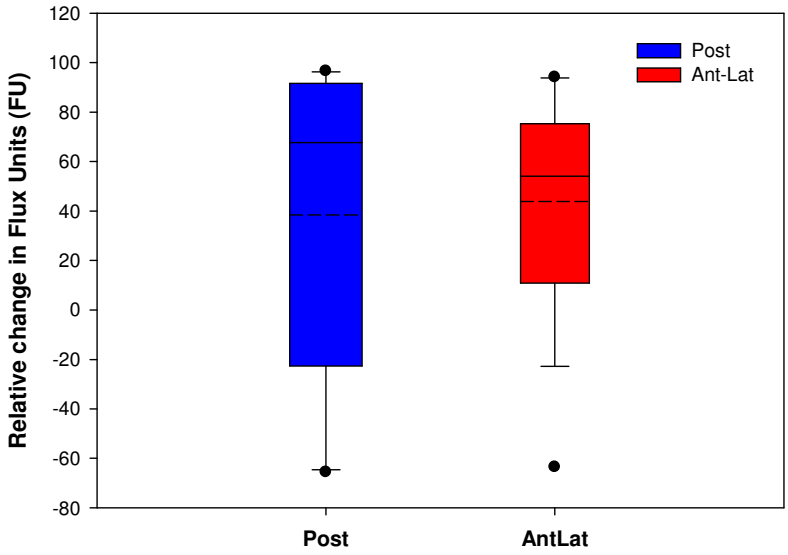


Figure 6.8: The box-plots show the results from the laser Doppler flowmetry measurements in the Post (blue box) and the AntLat (red box) group. The error bars represents the 95% limits, outliers are shown by black dots. The mean relative change (dashed line) and the median relative (solid line) change in blood flow are shown.

Study III

The results from the phantom study are shown in Table 6.4. We tested the precision between the three methods of analysis and found that marker-based was more precise than the CAD model-based regarding the total translation and the total rotation (TT, $p<0.001$ and TR, $p=0.01$) as well as the RE model-based (TT, $p=0.04$ and TR, $p<0.001$). When comparing CAD and RE model-based RSA, the RE model was more precise regarding the total translation (TT, $p<0.001$) whereas there was no difference regarding the total rotations (TR, $p=0.22$).

Table 6.4: RSA results from the phantom study comparing precision of RSA by marker-based and model-based (CAD and RE) analysis. Diff= difference between the serial stereo radiographs, SD= standard deviation, Min= minimum value, Max= maximum value.

Parameter	Marker-based RSA				Model-based RSA (CAD)				Model-based RSA (RE)			
	X	**Y**	**Z**	**TT**	**X**	**Y**	**Z**	**TT**	**X**	**Y**	**Z**	**TT**
Mean diff (mm)	0.00	0.01	-0.01	**0.07**	0.05	0.00	-0.01	**0.43**	0.03	-0.00	-0.04	**0.16**
SD diff (mm)	0.07	0.02	0.05	**0.03**	0.30	0.30	0.42	**0.38**	0.06	0.04	0.16	**0.08**
Min	-0.10	-0.02	-0.09	**0.03**	-0.50	-0.55	-0.50	**0.07**	-0.05	-0.07	-0.30	**0.05**
Max	0.12	0.04	0.06	**0.13**	0.55	0.56	0.83	**1.12**	0.16	0.07	0.16	**0.30**
	Rx	**Ry**	**Rz**	**TR**	**Rx**	**Ry**	**Rz**	**TR**	**Rx**	**Ry**	**Rz**	**TR**
Mean diff (°)	0.02	0.00	-0.02	**0.14**	0.29	0.23	0.31	**1.34**	0.08	0.08	0.01	**0.84**
SD diff (°)	0.09	0.11	0.05	**0.04**	1.10	1.12	0.65	**0.95**	0.67	0.68	0.44	**0.57**
Min	- 0.12	-0.13	-0.09	**0.08**	-1.14	-1.19	-0.53	**0.26**	-1.19	-1.25	-0.60	**0.13**
Max	0.16	0.14	0.07	**0.22**	2.25	2.32	1.29	**3.25**	0.90	0.92	0.58	**1.82**

Table 6.5: RSA results from the double analysis comparing marker-based and model-based RSA at 2 year follow-up. Diff= difference between the serial stereo radiographs, SD= standard deviation, Min= minimum value, Max= maximum value.

Parameter	**Marker-based RSA**				**Model-based RSA**			
	X	**Y**	**Z**	**TT**	**X**	**Y**	**Z**	**TT**
Mean (mm)	-0.08	0.05	-0.13	**0.24**	-0.12	0.10	0.16	**0.43**
SD (mm)	0.12	0.15	0.24	**0.23**	0.22	0.23	0.59	**0.53**
Min	-0.24	-0.07	-0.65	**0.08**	-0.59	-0.03	-0.45	**0.06**
Max	0.05	0.36	0.13	**0.78**	0.08	0.65	1.47	**1.71**
	Rx	**Ry**	**Rz**	**TR**	**Rx**	**Ry**	**Rz**	**TR**
Mean	-0.05	0.04	0.06	**0.99**	0.23	0.22	0.49	**0.85**
SD	0.58	1.34	0.25	**1.04**	0.71	0.58	0.76	**1.00**
Min	-0.59	-1.84	-0.12	**0.23**	-0.25	-0.33	-0.15	**0.04**
Max	1.26	2.84	0.61	**3.18**	1.90	1.24	2.12	**3.11**

Table 6.6: RSA results from the clinical data at the 5 year follow-up comparing marker-based and CAD model-based analysis. Diff= difference between the serial stereo radiographs, SD= standard deviation, Min= minimum value, Max= maximum value.

Parameter	**Marker-based RSA**				**Model-based RSA (CAD)**			
	X	**Y**	**Z**	**TT**	**X**	**Y**	**Z**	**TT**
Mean (mm)	0.02	0.04	-0.12	**0.61**	-0.13	-0.22	-0.17	**1.22**
SD (mm)	0.33	0.16	0.62	**0.38**	0.39	0.40	1.41	**0.88**
Min	-0.32	-0.21	-0.96	**0.09**	-0.49	-1.07	-2.10	**0.11**
Max	0.81	0.31	1.48	**1.49**	0.74	0.14	3.40	**3.57**
	Rx	**Ry**	**Rz**	**TR**	**Rx**	**Ry**	**Rz**	**TR**
Mean (˚)	-0.08	-0.26	0.10	**2.00**	0.34	-0.03	-0.08	**1.27**
SD (˚)	1.71	1.41	0.34	**0.90**	1.00	0.66	0.92	**0.81**
Min	-3.00	-2.00	-0.51	**0.93**	-1.71	-9.93	-1.46	**0.38**
Max	2.83	2.41	0.62	**3.61**	1.66	0.87	2.37	**2.98**

Second, we tested the clinical precision of marker-based and CAD model-based RSA and the results from the clinical precision in the double examinations (n=8) are presented in Table 6.5. The clinical precision was significantly better when evaluating the TT using the marker-based analysis (p=0.002) whereas there was no difference between the marker-based and CAD model-based regarding the TR (p=0.91).

Finally, we assessed the stability of the ReCap implant five years after surgery by as well marker-based as CAD model-based RSA. The results from the comparison of the marker-based and CAD model-based RSA (n=13) at the five-year follow-up are listed in Table 6.6. Furthermore, the migrations over time are shown for both methods in Figure 6.9 regarding the translations and rotations of all three axes.
Overall migrations were small with the greatest numbers seen in the rotations; however, rotations also had higher variations. The total translation was 0.61mm in the marker-based and 1.20mm in the CAD model-based analysis. The total rotation was 2.00˚in the marker-based and 1.21˚ in the CAD model-based RSA.
Comparing the mean signed values regarding TT and TR at five-year follow-up showed significantly lower TT in the marker-based analysis (p=0.02) and the TR was significantly higher in the marker-based analysis (p=0.01). No specific pattern was noticed regarding the translations in either the marker- based or the CAD model-based analysis. Results from the clinical examination and questionnaires are listed in Table 6.9. The mean HHS and OHS scores were equivalent to excellent and normal joint function, respectively.

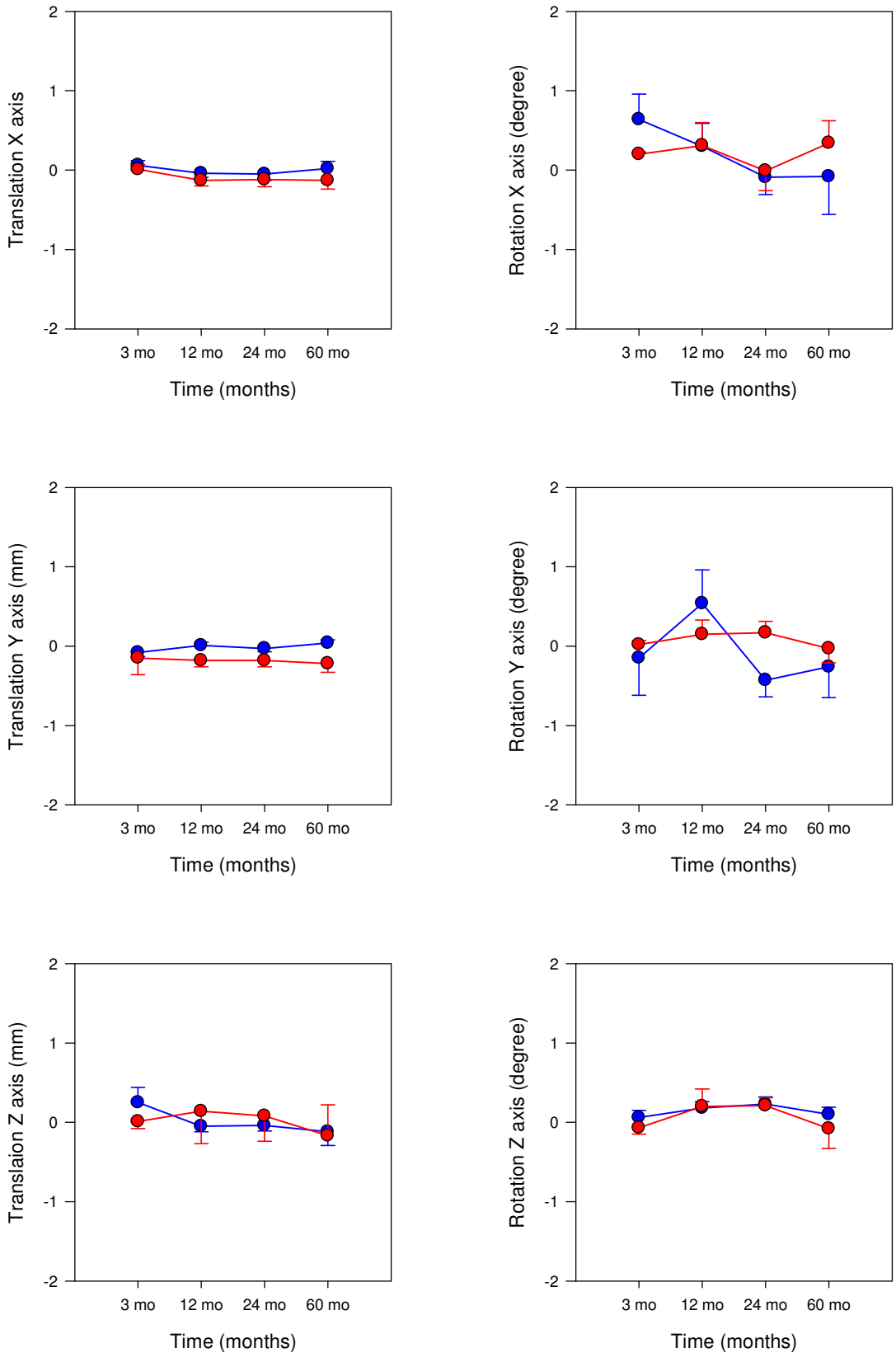


Figure 6.9: Translation (left) and rotation (right) along the x, y, and z axis measured in mm and degrees at the 5-year follow-up. The blue curve represents the marker-based RSA and the red curve represents the CAD model-based RSA. Error bars represents the standard error of the mean (SEM).

Study IV

MRI

The study population consisted of 44 patients of which 41 (18 ReCap and 23 MHE) of these patients participated in the MRI scan; two declined to participate, and one patient was exclude due to a pacemaker. The results from the MRI examinations are listed in Table 6.7. In the ReCap group, 11 of 18 patients had soft tissue lesions adjacent to the hip joint compared to only one of 23 patients in the MHE group, which was statistically significant (p=0.000).

Among the eleven ReCap hips with soft tissue lesions, four patients had one lesion and seven patients had two to four lesions resulting in a total of 21 solitary or two to three contiguous fluid-like collections located at the dorsal, lateral or ventral aspect of the femoral neck (see Figure 6.10). All lesions appeared with signal intensity (SI) corresponding to muscle on T1W (grade 1) and water on STIR sequences (grade 2). Two lesions demonstrated a peripheral capsule. The majority of the lesions were seen at the lateral or dorso-lateral aspect of the femoral neck. The mean size of all 11 soft tissue lesions in connection with the hip joint was 12x20x25 mm.

Furthermore two patients in the ReCap group demonstrated a bursitis: one at the greater trochanter and one in the iliopsoas compartment (see Figure 6.11). In the MHE Group only one of the 23 patients had a fluid-like collection at the ventral and lateral aspect of the femoral neck. Seven MHE implants had a bursitis; five at the greater trochanter (see Figure 6.12) and two in the iliopsoas compartment. Three MHE implants demonstrated changes in the bone marrow: one had a cystic lesion below the femoral stem and two patients had an area of edema also localized below the femoral stem. In the ReCap group muscle atrophy was seen as follows: glutei muscle (n=2), obturator ext (n= 6), obturator internus (n=12) and gemelli (n=12) and in the MHE group: glutei (n= 3), obturator externus (n=13), obturator internus (n=17) and gemelli (n=2, however, 21 could not be assessed due to artifacts). The cross-sectional area of the femoral muscles is listed in Table 6.7. We found no difference between the two groups, when comparing the difference in the muscle axial area between the operated and non-operated hip (p=0.38) and no difference between operated and non-operated hip in either the ReCap (p=0.75) or the MHE group (p=0.27).

Table 6.7: Results from MRI scan at the five-year follow-up. The muscle area is stated as group means and ranges in parenthesis.

	ReCap	MHE
Total number of hips	18	23
Soft tissues		
Normal soft tissue	7	15
Iliopsoas bursitis	1	2
Greater trochanter bursitis	1	5
Fluid-like collections	11 (21)*	1
Muscle atrophy		
Gluteus maximus		
Grade 0	17	22
Grade 1	0	1
Grade 2	1	0
Grade 3	0	0
Gluteus medius		
Grade 0	17	22
Grade 1	1	1
Grade 2	0	0
Grade 3	0	0
Gluteus minimus		
Grade 0	16	20
Grade 1	2	2
Grade 2	0	1
Grade 3	0	0
Obturator externus		
Grade 0	12	10
Grade 1	2	5
Grade 2	4	5
Grade 3	0	3
Obturator internus		
Grade 0	6	6
Grade 1	6	4
Grade 2	1	6
Grade 3	5	7
Gemelli		
Grade 0	6	0
Grade 1	2	1
Grade 2	4	0
Grade 3	3	1
NA	3	21
Bone-marrow		
Normal	18	20
Cystic formation	0	1
Edema	0	2
Muscle axial area (mm^2)		
Right hip	**12184** (9868-15333)	**12141** (9398-19048)
Left hip	**12265** (9643-14564)	**12270** (9692-18996)

*) In 11 of the ReCap patients more than 2 fluid-like collections were registered resulting in a total of 21 lesions.

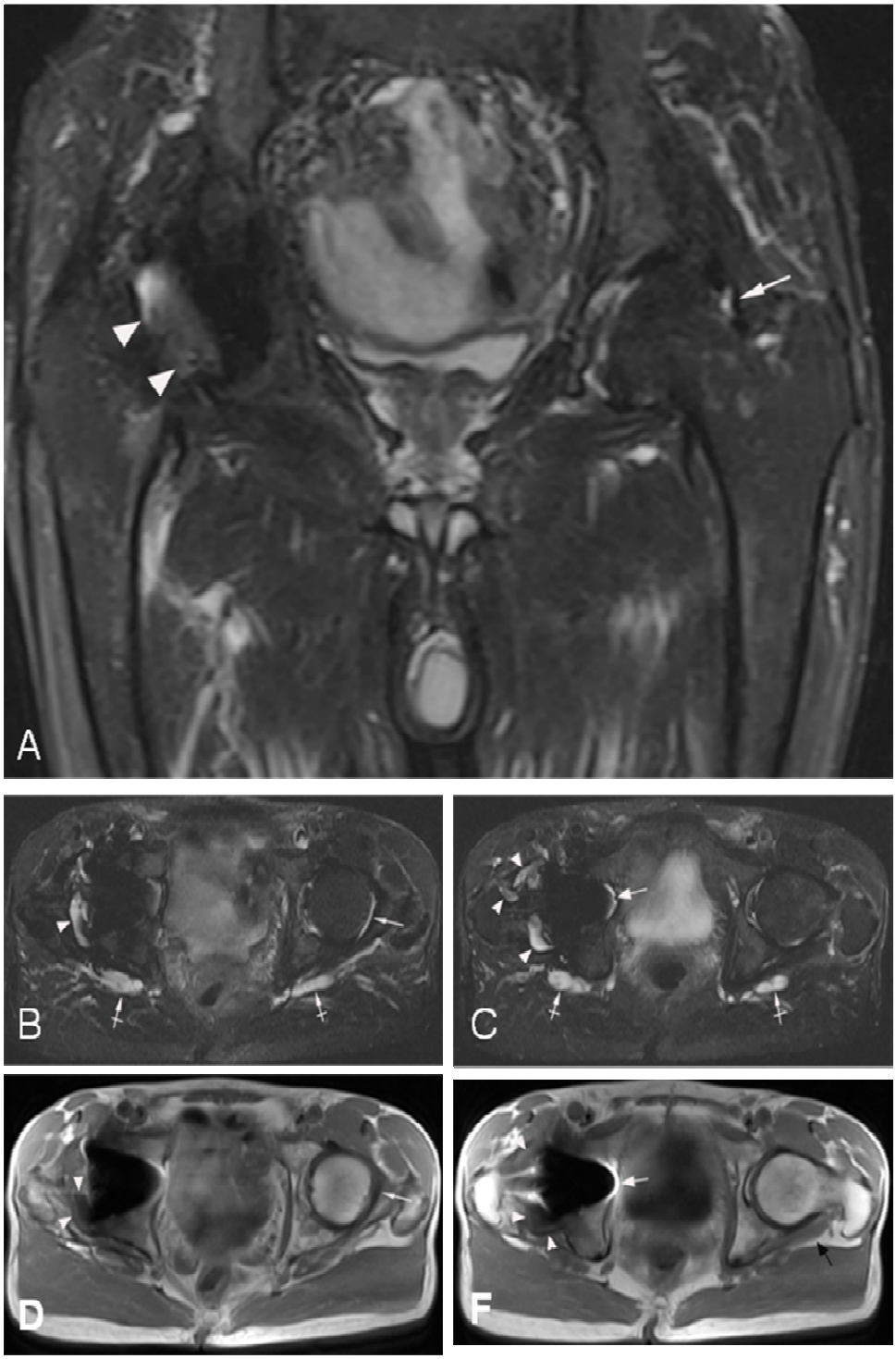


Figure 6.10. Characteristics of fluid like collections around the femoral neck in a right MOM THR. (A) Coronal STIR, (B and C) axial STIR and (D and F) axial T1 weighted MR images in a 66 year-old male. The fluid like collection surrounding the femoral neck (white arrowheads) demonstrates high SI, grade 2 on the STIR sequences (A, B, C) and intermediate SI, grade 1 on T1 weighted images. T1 weighted image may demonstrate a capsule in the periphery of the fluid like collection (D and F). White arrows (A, B and D), mild synovial fluid collection of the left femoral head and neck (A, B, D); white arrow, broad head, metal artifacts with high SI on STIR and T1 sequences (C,F); black arrow, normal superior gemellus muscle (F); crossed arrows, normal veins (B,C).

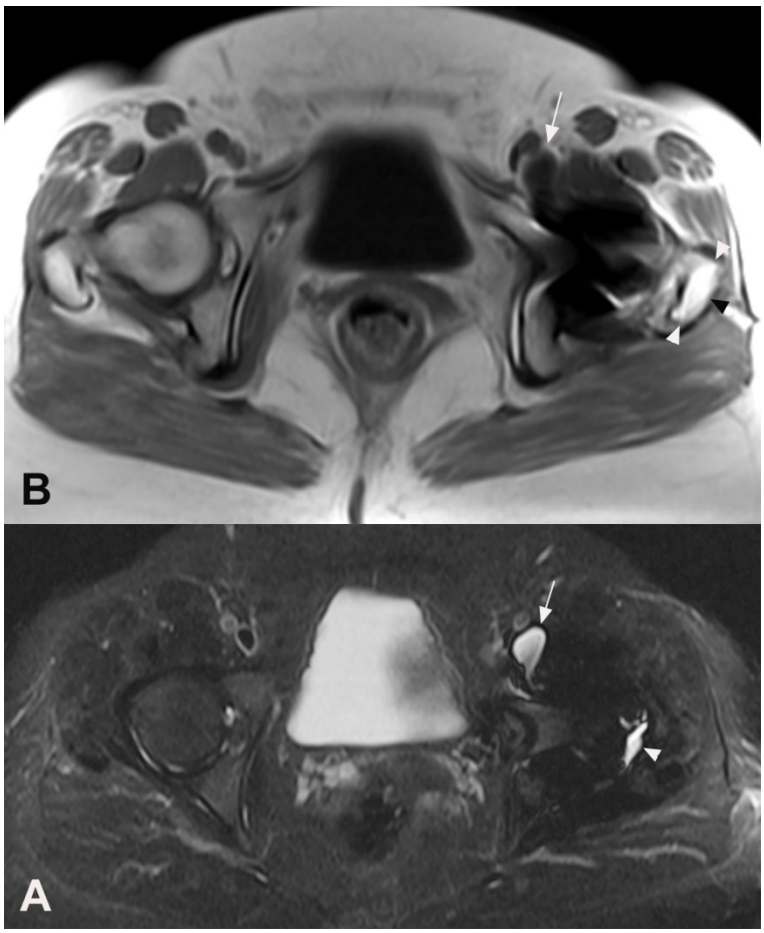


Figure 6.11. The figure shows an iliopsoas bursitis and metal artifact of the greater trochanter, on the axial MR images of a left MOM THR in a 62 year-old female. ***(A)*** *STIR and high SI, grade 2 of fluid collection (arrow) within an iliopsoas bursa.* ***(B)*** *T1 weighted sequence demonstrating intermediate signal, grade 1 of the iliopsoas bursitis (arrow). Arrow heads show metal artifact with high SI on both STIR (A) and T1 (B) sequence.*

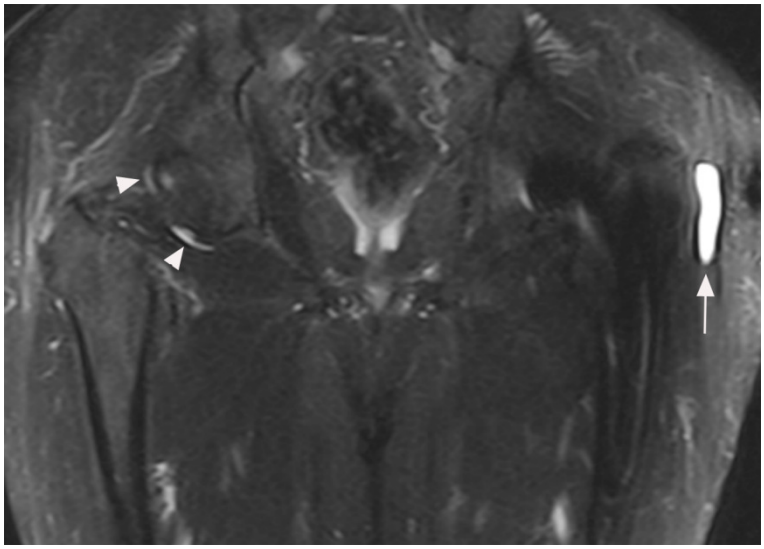


Figure 6.12. The figure shows a large trochanter bursitis, on the axial STIR sequence of left Exeter THR in a 69 year-old male. The arrow shows the fluid collection in the trochanter bursa; arrow heads show a mild synovial fluid collection around the right femoral neck.

DXA

The results from DXA scan showing the relative change in BMD from baseline (post-operative) to one, two, and five years after surgery regarding the seven Gruen zones are plotted in Figures 6.13 and 6.14. In the MHE group BMD in Gruen zone 1 increased during the first year and remained above baseline five years after surgery, whereas the BMD in all other Gruen zones decreased after surgery to a level that remained constant between one and five years after surgery. The decrease was most pronounced in Gruen zones 6 and 7 corresponding to the calcar region of the femoral bone. In the ReCap group BMD in all seven Gruen zones increased during the first year after surgery and to a level that remained constant between one and five years after surgery. The greatest BMD increase was seen in Gruen zones 1 and 2 in the cranial part of the femoral neck.

The results for the mean muscle and fat masses in the proximal femoral region as measured by DXA are listed in Table 6.9. In the CR we found the mean muscle mass were significantly lower in the MHE group compared to the ReCap group. Furthermore, the mean muscle mass was lower in the MHE compared to the control hips ($p<0.0001$), whereas the mean muscle mass in the ReCap group compared to control hips was similar ($p=0.795$). We found no significant difference between the mean fat mass in the ReCap and the MHE group. Also, we found no difference regarding the mean fat mass in the control hips compared to the MHE group ($p=0.23$) and the ReCap group ($p=0.11$). In OR the mean muscle mass was significantly lower in the MHE group compared to the ReCap group. There was significantly lower mean muscle mass in the MHE group compared to control hips ($p<0.0001$) and in the ReCap group compared to the control hips ($p<0.0001$). Regarding the mean fat mass, no difference was found between the MHE and the ReCap group but the mean fat mass was lower in the control hips compared to the MHE group ($p=0.001$) as well as the ReCap group ($p=0.001$).

The CV% for the double DXA examination (Gruen zones) as well as the CV% for the double analysis when templating the CR and OR to the Total Body Scan (intra-observer variance) are listed in Table 6.8.

Coefficient of variation (CV%)	ReCap	MHE	Control
Double DXA examination			
Gruen zone 1	3.10	1.48	
Gruen zone 2	2.08	2.17	
Gruen zone 3	2.44	1.05	
Gruen zone 4	0.75	0.99	
Gruen zone 5	2.11	1.84	
Gruen zone 6	1.87	1.50	
Gruen zone 7	3.82	1.50	
Double analysis of ROI templating			
OR fat mass	5.14	4.20	3.21
OR muscle mass	2.25	2.54	2.16
CR fat mass	1.04	2.80	3.74
CR muscle mass	2.26	2.61	3.92

Table 6.8: Coefficient of variation (CV%) from the double examinations from the DXA scan at two-year follow-up and the double examination at five-year follow-up.

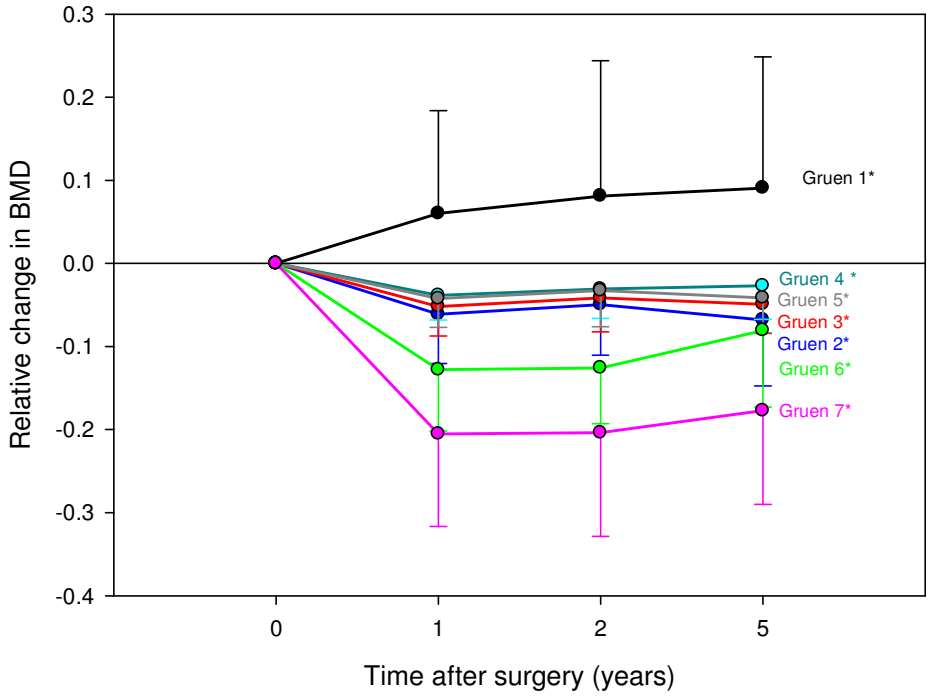


*Figure 6.13. Relative change in BMD from baseline to one, two, and five years after surgery in the MHE group. BMD is stated in g/cm². Error bars represents the standard deviation, *= p-value< 0.05 at five-year follow-up.*

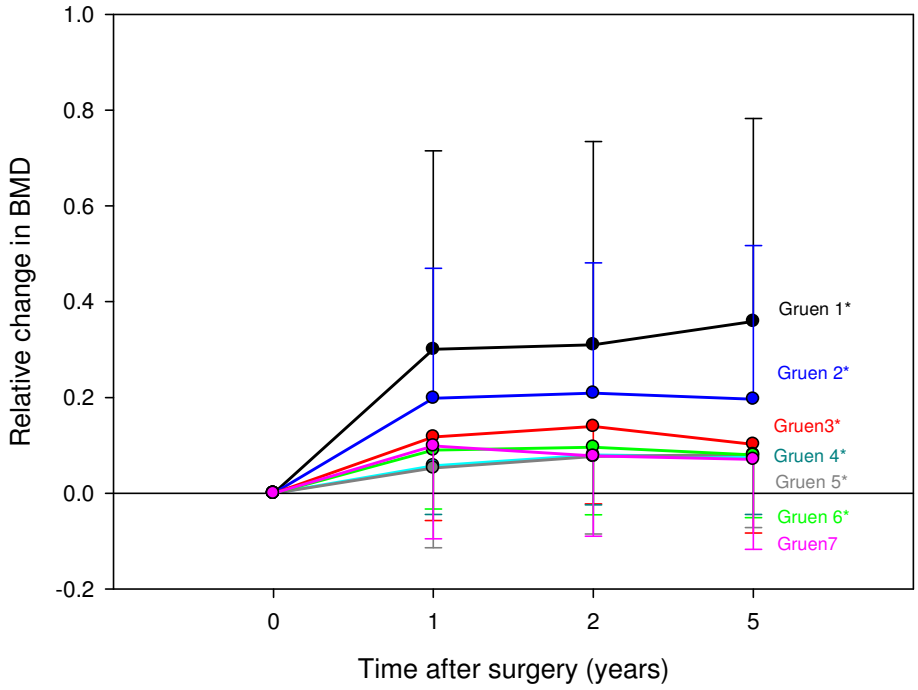


*Figure 6.14. Relative change in BMD from baseline to one, two and five years after surgery in the ReCap group. BMD is stated in g/cm². Error bars represents the standard deviation, *= p-value< 0.05 at five-year follow-up.*

Radiographs

When evaluating the post-operative radiograph compared to the radiograph at the five-year follow-up we found eight patients in the ReCap group with normal bone tissue. In two patients we found radiolucency lines>1mm in the DeLee zone 2. In six patients we found expansile osteolysis in the Gruen zones (predominantly zone 1-3) and in even patients we found expansile osteolysis in the DeLee zones (predominantly zone 1-2). Four patients had expansile osteolysis in as well the Gruen zones as the DeLee zones.

In the MHE group, 12 patients had normal bone tissue. We found radiolucency lines>1mm in two patients (Gruen zone 2) and expansile osteolysis in 11 patients all in the DeLee zones (predominantly zone 1-2). Implant position as well as acetabular inclination and anteversion angles are listed in table 6.9. There were no differences between the groups.

Clinical evaluation

There were seven patients with ReCap implants and one patient with a MHE implant who declined to attend the five-year follow-up. They were contacted by phone and four reported no pain or other symptoms, one patient had been revised due to a femoral neck fracture and three patients did not reply. Patient demographics and results from the clinical scores at the five-year follow-up are listed in Table 6.9.

We found no difference between the groups regarding the mean VAS, HHS or OHS score at five-year follow-up. The mean scores from HHS and OHS in the two groups were corresponded to excellent and normal joint function, respectively. Of the 44 patients, 35 were satisfied or very satisfied and four patients were not satisfied (three ReCap and one MHE). In five patients satisfaction rates were missing. The ROM was not different between the groups regarding extension, flexion, and abduction; whereas the adduction as well as internal and external rotation was significantly lower in the ReCap group.

Table 6.9. Patient demographics and DXA and MRI results from study III & IV

	ReCap	MHE	p-value
CLINICAL RESULTS			
Mean OHS (maximum 48)	45 (4)	44 (5)	0.57
Mean VAS (maximum 10)	0.5 (0.8)	0.7 (1.3)	0.72
Mean HHS (maximum 100)	94 (10)	96 (6)	0.40
Mean range of motion (degree)			
Extension	0 (0)	0 (0)	1.00
Flexion	95.8 (11.7)	101.6 (10.2)	0.08
Abduction	34.7 (5.9)	35.6 (6.7)	0.66
Adduction	23.7 (5.2)	28.2 (8.0)	0.04
Internal rotation	14.5 (8.1)	19.2 (6.7)	0.04
External rotation	16.6 (8.7)	22.4 (9.6)	0.04
RADIOLOGIC RESULTS			
Mean AC cup inclination angle (˚)	65.9 (59.1-86.4)	60.3 (35.4-75.0)	0.08
Mean anteversion angle (˚)	7.5 (1.8-17.3)	8.8 (2.0-25.1)	0.59
Heterotopic ossifications (No)	10	14	0.82
Femoral stem position			
Neutral	13	23	
Valgus	5	2	
Varus	1	0	
BMD MEASUREMENTS			
Total T-score	0.0 (-1.8;2.4)	0.0 (-2.9;3.2)	
Minimum T-score	- 0.72 (-3.2;2.1)	- 0.67 (-3.3;2.2)	
Oblong ROI (OR)			
muscle (g)	3188.56 (480.69)	2712.63 (472.75)	0.002
fat (g)	1236.61 (551.02)	1335.56 (466.28)	0.52
Circular ROI (CR)			
muscle (g)	1128.87 (208.42)	980.03 (202.42)	0.01
fat (g)	584.20 (244.43)	632.52 (178.13)	0.45

7. Discussion

Key findings

Study I
The meta-analysis showed a risk ratio (RR) of 1.86 regarding revision of HRA implants compared to THA implants. In the studies comparing HRA implants to THA implants, aseptic loosening was the most frequent cause for failure in both HRA and THA implants; however, in HRA the loosening appeared more often at the femoral component than the acetabular component. The single series evaluating HRA implants found femoral neck fracture to be the most frequent cause for failure followed by aseptic loosening of the implant.

Study II
The continuous evaluation of the metabolism in the femoral head and neck using microdialysis showed a significantly higher L/P and L/G ratio in the Post group compared to the Ant-Lat group indicating that the level of ischemia was higher in the AntLat group. There was no difference between the groups regarding the mean concentrations of glucose, lactate, glycerol and pyruvate. Also, we found no difference between the groups regarding the change in blood flow during surgery.

Study III
In the phantom study we found that marker-based RSA had the best precision followed by the RE model and CAD model which were equally precise regarding total rotation, but the RE model was more precise regarding total translation. The clinical precision of the double analysis showed significantly better precision using the marker-based analysis in the translations whereas no difference was found between marker-based and CAD model-based RSA regarding the total rotations. The HRA implants in the current study were stable all the way to the five-year follow up.

Study IV
We found a statistical significant increase in the number of fluid–like collections surrounding hip resurfacing implants (ReCap) compared with conventional THA (MHE). Second, we found that patients with HRA had an increased peri-prosthetic BMD in the femoral neck five years after surgery. Third, we found the muscle mass was reduced in both ReCap and MHE implants, but the reduction was greater in MHE hips compared to ReCap hips. Finally, the range of motion in the ReCap patients was significantly lower regarding adduction and rotations compared to MHE hips. However, all patients were satisfied with the results.

Discussion of results and comparison with literature

FAILURE RATE IN HRA COMPARED TO THA

HRA has higher failure rates compared to cementless THA

The second-generation HRA has been commercially available since the late 1990s and until now, studies and registries have reported data from nine-twelve years for follow-up (3;9;10;21;175). In the meta-analysis (Study I), in the studies comparing HRA and THA (group 2), we found the failure rate to be higher among the HRA implants, with a risk ratio of 1.86 (p=0.05). In the studies reporting data from single series of HRA (group 1), which we included in the review, the failure rate ranged between 0.2% and 7.0%.

In the Danish Hip Arthroplasty Registry annual report of 2010, the HRA implants represented 2.3% of all hip implants in 2009 and the five-year survival rate of HRA was 94%. The corresponding five-year survival rate of a cementless THA was 96% (4), which would be the alternative choice of treatment for patients receiving a HRA implant. The Australian National Joint Registry (AOANJR) annual report of 2010 HRA implants represented 7.2% of all hip implant and the five-year and nine-year revision rate was 4.2% and 7.4%, respectively. The nine-year revision rate in cementless THA was 5.2% (3). Finally, in UK the annual report from 2010, HRA represented 6% of all hip implants and they found a five-year revision rate in HRA of 6.3% compared to 3.4% in cementless THA (5). Similarly, Springer et al reported a failure rate of 2.6% in HRA implants after 3.9 years of follow-up due to aseptic loosening in the femoral component and 1.3% in the THA patients at 8.4 years of follow-up (160). The results from the above mentioned studies and registries are in line with the findings of our review and support our hypothesis in study I that HRA implants have higher failure rates compared to cementless THA implants.

The failure rates in the national registries are based on different brands which again perform differently in the follow-up. In both the Danish, Australian, and British national joint registries, the Birmingham Hip (Biomet Inc.) has demonstrated the lowest five-year revision rate (3-4%) whereas the ASR implant (DePuy) has demonstrated the highest five-year revision rate (10-12%), which is why this brand has been recalled from the market with the failures being caused by excessive rim wear (2-5). Still, in the Australian (AOANJR) 2010 report, "other" brands also demonstrated revision rates of 10%.

In study I we compared HRA to a cementless THA, which is the gold standard THA in Denmark today. In 1995, 70% of all Danish hip implants were cemented and only 10% were cementless, in 2002 there were more cementless hip implants inserted than cemented implants and in 2009, 67% were cementless and 15% were cemented implants. Also, the registry data from Denmark, UK and Australia show that the failure rate in HRA is almost a factor of two higher than the corresponding failure rates in cementless THA.

Studies have demonstrated that the surgeons' learning curve can possibly cause higher revision rates in HRA (125;132;194), patient selection is important to achieve a long survival of the implant (150), and data from the Australian registry (AOANJR) in 2010 have demonstrated that femoral component sizes of 44 mm or less and male patients older than 65 years at surgery have higher revision risk (3). Since the brand

demonstrating the highest failure rates have been recalled from the market and focus has now been directed towards meticulous patient selection and surgical technique, these steps could possibly improve the implant survival. In the coming years we will know if the remaining HRA brands will still have an elevated revision rate or will demonstrate a revision rate which will settle at the revision rate seen in cementless THA implants.

CAUSES FOR FAILURE IN HRA

Aseptic loosening, osteolysis, and wear

In the review (study I) we found that aseptic loosening of the implant was the second most frequent cause of failure among the single series of HRA reports (group 1) and in the THA implants in studies comparing HRA and THA (group 2). In the HRA implants in group 2, aseptic loosening was the single most frequently reported cause for failure. In study IV the assessment of radiographs showed that expansile osteolysis was more frequent than radiolucency lines in both the ReCap (HRA) and MHE (THA) group. Furthermore, in the ReCap group osteolysis was present around the acetabular as well as the femoral component, whereas in the MHE group osteolysis was only seen around the acetabular component.

The reason for aseptic loosening in MOP implants is well established as wear of the poly-ethylene produces wear particles that induce osteolysis and implant loosening (55;119). Young patients bear a higher risk of aseptic loosening since their level of activity is higher compared to older patients, which again results in a greater production of wear particles due to the increased wear on the implant bearing surfaces. The metal-on-metal (MOM) articulation has been designed to produce a more durable and wear-resistant alternative to the MOP.

MOM bearings have been used in both HRA and THA implants and have showed acceptable survival rates (81;83;119;175). Despite MOM being more resistant to wear, this bearing material produces larger amounts of wear particles, which also differ considerably in size compared to polyethylene particles. Studies have analyzed MOM implants and found a mean wear of 25 µm within the first year, which then decreased to 5 µm in the following years. This wear rate is 20 times less compared to the wear rate in MOP implants. Also, the mean size of the MOM wear particles was considerably smaller (50-100 nm) compared to the mean size of MOP wear particles known to induce aseptic loosening (0.5 - 1.0 µm). In addition to the smaller wear the MOM wear particles are 1000 times smaller compared to MOP wear particles. This means that MOM implants produce larger numbers of wear particles compared to MOP implants, even though the measured amount of wear is smaller (54;157). Also, due to the small size of MOM wear particles, it is unclear whether they are able to stimulate the biological pathways in the same way as MOP wear particles which is a macrophage-induced simulation resulting in increased activity of osteoclastic cells and a decreased activity of the osteoblastic cells leading to bone resorption and osteolysis and possible implant loosening (157).

The results from study I show that aseptic loosening is still a major problem and a frequent cause of failure leading to implant failure in HRA implants. Also, the results from the five-year follow-up on HRA implants (study IV) support this by demonstrating that osteolysis, which could lead to aseptic loosening was seen in

47% in the ReCap group and 44% in the MHE group. However, the results from the migration studies using RSA (study III) showed that the HRA implants were stable five years after surgery and so far, the osteolysis we have assessed on the radiographs have not resulted in migration patterns which would indicate that the implants are failing.

Femoral neck fracture and avascular necrosis

Femoral neck fracture and avascular necrosis of the femoral neck will eventually lead to implant failure. Several theoretical considerations concerning the causes of these complications have been proposed, including a reduced strength of the femoral neck caused by the surgical preparation for the femoral component, the position of the inserted femoral component, and the possible effect of the surgical approach on the blood flow to the femoral head and neck (7;46;144). In the review (study I), femoral neck fracture was the most frequent cause of failure in 18 of 21 studies in the single series of HRA reports (group 1), accounting for 35.4% of all failures. In the HRA implants in the studies comparing HRA and THA (group 2), femoral neck fracture was the second most frequently reported complication, accounting for 30.6% of reported failures.

The results from our review (study I) correspond with data from the Australian (AOANJR) report from 2010 where femoral neck fracture accounted for 36% of all failures in HRA (3). In the review we did not find adequate information to evaluate weather notching of the femoral neck was the reason for the femoral neck fractures, however, Davis et al (46) showed that notching of the femoral neck would reduce the strength and elevate the risk of femoral neck fracture, and Vail et al demonstrated that notching of the superior part of the femoral neck resulted in a decrease in femoral neck strain by 21% (182).

In study IV the five-year follow-up radiographs on the HRA implants showed valgus orientation in five of 19 patients and varus orientation in one patient on the AP radiograph. Furthermore, in three patients a notching in the superior part of the femoral neck was seen on the radiographs: however, no fractures have been registered in these patients. Richards et al found a significant increase in failure load for valgus-oriented components compared to neutrally positioned components (144) and Siebel et al reported a significant correlation between notching of the femoral neck and failure (156). In study IV one patient was excluded from the study due to a femoral neck fracture, whereas the remaining patients showed no signs of fracture or loosening of the implants (study III and IV).

Apart from inappropriate implant positioning and notching of the femoral neck during the surgical preparation, development of avascular necrosis in the femoral head and neck could be another possible explanation for femoral neck fractures seen post-operatively. In the review (study I) we found avascular necrosis was reported in 11 of the 27 studies. In study II, we demonstrated that the reaming process and the cementation of the implant resulted in a decrease in the perfusion of the femoral head and neck in eight out of 11 patients in patients operated by the posterior approach and in 14 out of 17 in the patients operated by the antero-lateral approach, however, there was no statistical difference in the blood flow changes between the two surgical approaches.

Studies have demonstrated a 40-70% reduction in the blood flow when using the posterior surgical approach compared to an 11% reduction in blood flow when using the antero-lateral approach (7) and Beaulé et al demonstrated a reduction of more than 50% in blood flow after notching the femoral neck (149). A lasting decrease in blood flow may induce a necrosis of the femoral head, but so far, only measurements of blood flow during surgery as well as results from PET scans one and two years after surgery have been published (177;178).
The results from the microdialysis in study II showed ischemia in the femoral head and neck in all patients after surgery, but the increase was greatest in the group operated by the posterior surgical approach. This indicates that a possible decrease in blood flow initiated during surgery is persistent at least within the first two to three days after surgery. Decreased blood flow seen during surgery could also be explained by the different positions of the leg during surgery as both Nötzli et al and Steffen et al have demonstrated that the dislocation of the hip joint and the different leg positions during surgery influences the blood flow in the femoral head and neck (131;161). A temporary interruption of the blood flow will only lead to a decrease of the perfusion during surgery and then the perfusion even in bone would be expected to return to the pre-operative levels, as demonstrated in muscle tissue by Korth et al (101).
Curing of bone cement is known to induce an increase in the temperature of the surrounding tissue and the cementation of the femoral component could possibly initiate a temporary or permanent decrease in the perfusion due to thermal injuries to the bone tissue and vessels. The curing temperature of Simplex bone (used in Study II and IV) cement is 60° at the bone cement interface, but as high as 95° in the core. Beaulé et al and Little et al have demonstrated that a thicker cement mantle is seen in ReCap implants compared to other HRA brands and that implants with thick cement mantles show higher temperatures when settling (22;108). Therefore, thermal damage could possibly increase the level of an existing ischemia (relative or absolute) initiated due to choice of the surgical approach when implanting HRA implants.

THE POSTERIOR SURGICAL APPROACH RESULTS IN MORE ISCHEMIA IN THE FEMORAL HEAD AND NECK

Ischemia in bone tissue

Tissues which are sufficiently perfused will receive adequate amounts of oxygen as well as substrates. If the perfusion is inadequate, ischemia and hypoxia can occur. Ischemia is defined as a standstill in the blood flow. A standstill of the blood flow can be absolute or relative, and the reason for the standstill in the blood flow can be either an arterial or a venous obstruction. The definition of ischemia includes a reduction in the supply of oxygen as well as in the supply of substrates in the tissues. Hypoxia, which is defined as an insufficient supply of oxygen, is a part of ischemia. Hypoxia can be caused by other than a standstill in the blood flow, such as an increased demand in the tissue or a respiratory insufficiency. The consequence of hypoxia is an increase in the content of lactate (due to anaerobic metabolism) and an increase in the lactate/pyruvate (L/P) ratio, which represents the redox-potential of the tissue.
In addition to these changes, the consequence of ischemia includes a decrease in the content of glucose resulting in an elevated lactate/glucose (L/G) ratio. Together with

the content of glucose, the estimation of the L/G ratio may allow to determine whether the case is hypoxia or ischemia. No validated results for the L/G ratio exist for bone tissue. However, very stable low concentrations of glucose indicate absolute ischemia, whereas a circadian rhythm in the glucose concentrations indicates that the ischemia is not absolute and that maybe only hypoxia is the case. Generally, a glucose concentration below 1 mmol/L and a lactate concentration above 2 mmol/L as well as a L/P ratio above 25 is considered to represent ischemia (181). When hypoxia or ischemia is severe enough to induce cell death, the destruction of the cell membrane will result in an increase in the glycerol concentration. When performing microdialysis the absolute values of the metabolic markers can be used to evaluate the metabolism in the tissue, however, the trends and changes in these values as well as the ratios between the metabolic markers are important as well.

The choice of surgical approach influences the blood flow and metabolism in the femoral head and neck

Microdialysis (MD) has previously been used to measure the perfusion of bone tissue in experimental studies as well as to measure the level of antibiotics in bone and muscle tissue as demonstrated by Bøgehøj et al and Stolle et al (29;30;110;171). Until now, a continuous monitoring of the metabolism in the human femoral head in the post-operative period is novel and has not previously been described in the literature of orthopedic surgery. The choice of surgical approach can possibly affect the blood flow to the femoral head and neck since the medial circumflex artery, which is the main blood supply to the femoral head and neck, runs on the posterior part of the femoral joint capsule and is often ligated during surgery when performing the posterior surgical approach.

The posterior approach is the standard approach in Denmark, UK and Australia (3-5) whereas only 60% of hip surgeries are performed through the posterior approach in Sweden and only 24% in Norway (79). On the contrary, when performing the antero-lateral approach the artery is not affected by the surgical procedure. If the posterior approach results in a persistent decrease in the perfusion, we would expect to see a shift towards an anaerobic environment in the bone tissue. In study II, we found the L/P and the L/G ratios were elevated in as well the Post group (posterior surgical approach) as the AntLat group (anterolateral surgical approach); however, the increase was higher in the Post group. This indicated that the metabolism in the femoral head and neck was more influenced in this group compared to the AntLat group. In seven of nine patients in the Post group and in 14 of 15 patients in the AntLat group, we labeled the metabolism in the tissue relatively ischemic after finding a circadian rhythm regarding the glucose concentrations which caused us to presume that the bone received some amount of perfusion (see Figure x). However, the patients who had a relative ischemia in the femoral bone also showed high lactate concentrations. This could be due to either an increased demand in the tissue despite an adequate perfusion or a perfusion which is lower than normal combined with a normal demand of nutrients in the tissue. As we did not have a baseline measurement before the beginning of the surgery and furthermore lacked knowledge from previous research of microdialysis in bone tissue, we do not know whether

these substrate concentrations differ significantly from normal levels of the substrates in bone tissue.
In two of the nine patients among the patients operated upon by the posterior approach and one of the 14 patients among the patients operated by the antero-lateral surgical approach, we labeled the metabolism as absolutely ischemic as it did not show any sign of circadian rhythm regarding the glucose concentrations and presented a continued low glucose and high lactate levels. However, they also showed relatively high lactate concentrations, and this could be due to either an increased demand in the tissue despite the perfusion remains unchanged. As demonstrated in Figure x the L/P ratio was elevated in all patients, both the relative and the absolutely ischemic, but the L/G ratio was higher in the absolute ischemic patients compared to the relatively ischemic patients. Setälä et al demonstrated that a relatively higher L/P ratio compared to the L/G ratio could indicate an arterial rather than venous occlusion (153).
Because there has been no previous research, it is unclear whether the alterations in metabolism that we have demonstrated are due to relative or a partial or total arterial occlusion or due to a venous congestion. Whether the metabolic changes are large enough to produce a permanent damage to the cells and induce an area of osteonecrosis or fracture can be demonstrated by following these patients in the future and registering whether any complications will occur or by performing a PET scan to assess areas of osteonecrosis in the femoral head and neck. Nevertheless, as we found signs of absolute ischemia in only two of nine patients operated upon by the posterior surgical approach and one of 14 patients operated upon by the antero-lateral surgical approach, our results do not indicate that any specific surgical approach induces absolute ischemia in the femoral head. Based on the results from the microdialysis we can support our hypothesis from study II that the posterior surgical approach induces more ischemia in the femoral head and neck compared to the antero-lateral surgical approach.

Other metabolites to use as markers of ischemia in the bone
Glycerol is another possible marker of metabolism to use in the evaluation of ischemia in tissues. Glycerol does not directly reflect the metabolism, but only demonstrates the amount which is released from the cell membrane. If the perfusion is decreased to an extent leading to cell death, the breakdown of the cell membrane will result in an increased release of glycerol into the interstitial tissues.
Elevated concentrations of glycerol could be explained by different situations. Thus, a high concentration could be explained by cell membrane damage due to drilling in the bone or a period of hypoxia or ischemia initiated by a reduced perfusion, resulting in cell death and subsequent release of glycerol from the cell membrane. In case of damage due to drilling in the bone, we would expect the release of glycerol to decrease as the glycerol is washed out and the damage has only been temporary. In case of hypoxia or ischemia, the release of glycerol will continue as long as the cell death is ongoing. However, high glycerol concentrations could also be explained by a continued high release despite a sufficient perfusion of the tissue as long as the relative increase in release of glycerol is higher than the perfusion. Finally, the concentration of glycerol could also be high if there is a decrease in the perfusion of

the tissue, combined with a decrease in the release of glycerol, as long as the decrease in the perfusion is larger than the decrease in the release of glycerol.
The results of the mean glycerol concentrations show an overall decline in the majority of patients operated by the posterior as well as the antero-lateral surgical approach. As demonstrated by Bøgehøj et al. (29;30), drilling in bone tissue results in elevated glycerol concentrations, as it is released because of damage to the cell membrane. For this reason, we expected the mean concentration of glycerol to be elevated or that it would rise within the first hours of measurement and afterwards to decline if there were not an absolute ischemic environment leading to continued high concentrations of glycerol released into the interstial tissue due to release from cell membrane breakdown. When comparing the absolute ischemic patients and the relative ischemic patients, we did not find different patterns regarding the glycerol concentration (study II). In both groups of patients, the glycerol concentration was high in the first hours after surgery, after which the concentration decreased in both groups of patients. This could indicate that the microdialysis measurements are artifacts and does not entirely reflect the metabolism in the femoral bone. Therefore, our findings should be interpreted based on this knowledge.

HRA IMPLANTS INDUCE A PHYSIOLOGIC LOAD TO THE FEMORAL BONE

BMD preservation around HRA and THA implants

In study IV, the femoral components used in the two groups (ReCap and MHE) are different in terms of design. In the MHE implants a greater part of the femoral bone is removed during surgery and the transmission of the patients load during stand and gait follows the implant to the diaphysis of the femoral bone. In the ReCap implant only the damaged cartilage surfaces and a small amount of the sub-cartilage bone are removed and the transmission of the patients load during standing and gait, transmitted from the implant to the femoral bone, is supposed to occur in a more physiologically natural way (99).
The periprosthetic bone of the two differently designed implants is anatomically not the same, and we found that a comparison of the Gruen zones between the two implants was irrelevant. However, we have analyzed peri-prosthetic BMD changes within each implant group separately. We could have assessed the diaphyseal femoral bone in the ReCap group (HRA) for direct comparison of the bone to the MHE (THA) implants, but decided not to do so because of the physiologic differences. In the ReCap group (HRA) we found the BMD to increase within the first year after surgery in all seven Gruen zones and remain stable until five years after surgery with the greatest increase in Gruen zone 1 and 2; whereas in the MHE group (THA) the mean BMD only increased in Gruen zone 1 and decreased in all remaining zones to a level that was stable between one and five years follow-up for all Gruen zones but with the greatest decrease in Gruen zone 6 and 7.
The majority of studies, which report peri-prosthetic BMD in Gruen zones as measured by DXA investigated cementless implants and showed a greater decrease in BMD in the proximal bone (Gruen zone 1 and 7) (28;187). Studies (43;52;106) of cemented implants report the most pronounced BMD decrease in Gruen zone 7, the calcare region. Bieger et al. compared BMD in cemented versus cementless stems and found similar results (25) which is in line with BMD measurements for a cemented traditional femoral stem. BMD measurements in HRA implants have shown that

BMD is preserved and/or even increased compared to baseline levels (41;78;99). In our study the increase in BMD seen in the HRA group was greatest in the cranial part of the femoral neck (Gruen zone 1 and 2) which may be explained by (72) elevated bone strain in the superior part of the neck as described by Gupta et al with a finite element model applying load equivalent to 70 kg and for prediction of bone remodeling based on an adaptive bone remodeling theory.
Our results suggest that the load on the femoral bone is more natural with a ReCap implant compared to a conventional implant, and, since BMD is preserved, may be able to prevent stress shielding and osteolysis in the bone around the HRA implants. Other authors have shown an accelerated BMD decrease in the first three to six months after surgery, possibly related to impaired weight-bearing and a decreased activity level and stress-shielding caused by load-transfer changes (41). In study IV the first follow-up measurement after surgery (baseline) is at one year and we may have missed early peaks of decreased BMD, yet we can show that the peri-prosthetic bone around a standard cemented femoral stem as well as the bone around a cemented HRA changes very little between one and five years after surgery. A minor decrease over the years after surgery is expected due to the physiological ageing of the bone tissue; however this change was very small as judged by our BMD results between one and five years after surgery. The results from study IV support the hypothesis that HRA implants transfers the load from the implant to the host bone in a more physiological way and thus preserve the BMD.

Pre-operative diagnosis, implant size and gender
Several studies have reported a correlation between the survival of HRA implants and patient-related factors–thus it is of great importance and concern to perform a proper patient selection (150). Factors that influence the outcome in HRA are the preoperative diagnosis (osteoarthritis versus osteonecrosis and dysplasia), component size, gender, and BMI. In the review (study I), the preoperative diagnosis was OA in the majority of patients in all 27 studies and so the failure rates we identified are based on osteoarthritis as the primary diagnosis. However, as we did not include studies which reported outcomes in HRA with other pre-operative diagnoses we have not been able to compare the outcome of primary osteoarthritis to the outcome of other pre-operative diagnoses.
Revell et al reported a failure rate of 6.8% at a mean follow-up of 6.1 years in a study on osteonecrosis as a primary diagnosis (142). Also, data from the Danish, Australian, and British national joint registries report that the majority of HRA implants are inserted due to primary osteoarthritis (3-5). Until now, little information has been published regarding the results of osteonecrosis and dysplasia as the primary diagnosis in HRA. In two studies, Amstutz et al reported results on dysplasia and osteoarthritis secondary to childhood disorders; the failure rates were reportedly 7.8% at a mean follow-up of six years, and 8% at a mean follow-up of 4.7 years (11;12), whereas a study by Mont et al, the failure rates were equal when comparing osteonecrosis to osteoarthritis after a follow-up of 3.4 years (123).
The size of the femoral component also seems important in terms of implant survival. In study I we identified five studies who reported a correlation between small component sizes and an increased risk of failure (88;117;134;172;175). These findings are consistent with data from the Australian National Joint Registry (2010), indicating that femoral component sizes less than 44 mm are associated with failure

of the implant as well as are male patients aged 65 years or older at the time of surgery (3). In the Australian registry females had a higher revision rate than male patients but this was due to the smaller component sizes inserted more often in woman. Also, no age related increased risk of revision was seen in woman. In study IV none of the patients included in the study received a component size of 44 mm or less, and the smallest femoral component size used was 46 mm which was inserted in five patients. Finally, in the review we found four studies that reported a correlation between obesity and failure (98;115;134;156). In conclusion, meticulous patient selection seems of great importance to achieve the best possible outcome in HRA implants.

HRA IMPLANTS ARE STABLE FIVE YEARS AFTER SURGERY

Precision of RSA in HRA implants

In the phantom study (study III), the RE model of the ReCap implant was a scanned model (reverse engineered from a laser scan) derived from the particular implant that we used and therefore is supposed to provide the best possible standard for the obtainable results using a model for RSA. When comparing the marker-based RSA as the gold-standard with the RE model-based RSA we found a similar standard deviation for the translations, whereas in comparison with the CAD model-based RSA, the standard deviations were an average 0.3 mm higher. When looking at the rotations, the RE model-based RSA had a SD that were approximately a factor of 12 times higher, whereas the CAD model-based RSA had a SD that were approximately 20 times higher compared to marker-based analysis. Based on the phantom study, where all images were optimal, meaning all implant and bone markers were visible as well as no soft-tissues shadowed the femoral head, and an optimal radiographic quality was obtained, we found the CAD model to have a remarkably poorer precision compared to marker-based and RE model-based analysis as judged by the standard deviations of repeated phantom examinations with repositioning of the phantom between each new stereo radiograph. This supports our hypothesis from Study III that marker-based RSA is more precise compared to model-based RSA.

The results from our clinical double examinations showed superior precision for the marker-based method compared with the CAD model-based regarding the translations whereas we found no significant difference between the methods regarding the rotations. The clinical precision was between a factor of two times poorer regarding the TT, and whereas we did not find difference between regarding the TR when comparing the marker-based and the CAD model-based RSA. Among other sources of error this relates to variation of marker dispersion among investigated patients and poor placement of the implant i.e. hidden implant markers on the stereo radiographs. Based on the double examination, the precision with a detection threshold of 0.5mm regarding TT for marker-based RSA and a detection threshold of 1mm TT for CAD model-based RSA can be estimated. Therefore we cannot conclude statistical differences in changes below these thresholds.
As demonstrated by Kärrholm (93), in hip arthroplasty, the migration of the femoral head with respect to the femoral bone of more than 0.85mm (total migration) and subsidence of 0.33mm was related to revision risk (93;147). Furthermore, subsidence

greater than two mm within the first two years after surgery was correlated to revision surgery. Given that similar sizes of continuous ReCap implant motion lead to implant failure, both RSA methods that we assessed should be able to detect the failing implants. Thus, both methods can be used for measurements of continuous TT above 1 mm as a predictor of implant failures by implant loosening.

Stability of HRA implants at five-year follow-up by marker-based and model-based RSA

In study III we validated the CAD model-based analysis for use in the migration-analysis of ReCap implants and found no systematic difference in signed mean migration values except for the Y-translation where marker-based RSA was superior. The systematic difference in mean (absolute) total translations (0.6 mm) and total rotations (0.8°), as was found at the five-year follow-up between the two methods, were small, but the random variations were better for the marker-based analysis regarding the total translations in the double examinations. Looking at the data from the patients at two-year follow-up, none of patients had migrations greater than 1mm using marker-based analysis whereas when using model-based analysis, two patients had migrations greater than 1mm. At the five-year follow-up, two patients had migrations greater than 1mm using marker-based analysis and the same two patients had migrations greater than 1mm using the model-based analysis. These patients could possibly risk an early loosening of the implant if using the criteria regarding risk of implant loosening found by Kärrholm (93). Marker-based RSA used on HRA implants has limitations since the implant markers must be placed on a very small size stem (centralizer) of the femoral component. Due to this, the implant markers are placed very close to each other (condition number 68) and this will hardly represent the center of the head and cup where the potential loosening of the implant will occur. The CAD model-based RSA may therefore represent a more clinically relevant model to use when measuring the motion of the total implant.

MOM WEAR PARTICLES AND RELATED COMPLICATIONS

Wear particles

The formation of MOM wear particles is well known and they can accumulate locally in the tissues surrounding the hip as well as being disseminated widespread in the organism (87). There are several reports of elevated serum concentrations of metal ions (ref) but so far no standardized guidelines have been developed to assess the limits of ion or metal wear particles that can be accepted. Also, no large-register studies have been able to document any obvious link between serious systemic diseases and MOM wear particle release (188).

There have been several studies reporting on benign soft tissue masses that can be locally destructive and erode into the femoral and acetabular bone. These soft tissue lesions with a histopathological presence termed ALVAL (giant-cell formation, accumulation of lymphocytes around vessels and tissue necrosis) have been found in the proximity of MOM implants (including HRA) and have been proposed to be inflammatory lesions possibly combined with allergic hypersensitivity reactions to metal wear debris (70;111;135;195). These soft tissue lesions developed around MOM

implants have been described by computed tomography (CT), ultrasound and MRI (76;148;195).

MOM soft tissue lesions on MRI

The MRI scans showed soft tissue lesions along the femoral neck in 11 of 18 patients in the ReCap group but only in one out of 23 patients in the MHE group. The SI of the soft tissue lesions indicated fluid-like collections and their general appearance resembled synovitis, synovial effusion in arthritis, or osteoarthritis of the hip joint. The frequency of the lesions correspond well with findings by Hart et al (cystic lesions in 54% of patients) and Sabah et al (cystic lesions in 74% of patients), who investigated unexplained painful hip HRA implants, and with results from Wynn-Jones et al (cystic lesions in 37% of patients), who investigated MOM implants in patients without complaints. They all described fluid signal collections as the most frequent finding in MOM hips (76;148;195), but the location and severity of lesions may be different from those observed in the present study.

We suggest that the fluid-like collections we found may represent synovitis secondary to accumulation of metal wear debris. The anatomical location and MR appearances of these lesions have to our knowledge not previously been described. Gadolinium contrast-enhanced MR imaging may be of value in future evaluations of these lesions; however, a synovial origin of the lesions can only be confirmed by histology. None of the patients that we assessed were seen because of referral for pain or poor function-they were all planned five-year controls. As the origin of the soft tissue lesions in MOM patients is not yet fully understood, reservation should be taken in the interpretation of the MRI findings. However, further investigation into the possible histological reactions to MOM wear particle is beyond the scope of this thesis.

RANGE OF MOTION AND PATIENT SATISFACTION IN HRA IMPLANTS

Muscle assessment on MRI and DXA

In study IV we performed an analysis of the femoral muscle mass on DXA and MRI scans. In the regions of interest in the DXA scans, we found the muscle mass to be significantly reduced in implant hips (ReCap and MHE) compared to non-operated hips. Furthermore, the muscle mass in MHE hips were significantly reduced compared to the ReCap hips. These findings correspond with the results from the MRI scans, where a majority of patients in the MHE group had atrophy of the rotator muscles surrounding the hip joint. However, atrophy of the glutei muscles were only seen in three patients.

When inserting the implant, the surgical approach differed only slightly, since both groups were operated by the posterior approach, although in the ReCap group, a partial detachment of the gluteus maximus insertion was performed since a larger incision was needed when inserting the implant. The detachment of the gluteus maximus muscle can possibly initiate the formation of fibrotic scar tissue which potentially can result in increased tension of gluteus maximus and thereby reduced range of motion, particularly rotation as was demonstrated in the ReCap group. Previously, MRI as well as DXA scans have been used to investigate and measure body composition in humans, including fat mass and muscle mass (97;120;154). In

MRI there is a specific signal intensity corresponding to muscle tissue. However, in DXA scans tissue measurements are divided into bone, fat and lean mass. The lean mass is often interpreted to be equivalent to the muscle mass. The validity of this comparison of the lean mass and the muscle mass has been demonstrated in several studies comparing muscle tissue measurements in MRI and DXA (33;34;56;64). These studies have demonstrated that results from the DXA scan often overestimate the lean mass tissue compared to results regarding the muscle mass measured on MRI. Therefore, caution should be taken when evaluating the results as we have reviewed methods that are not entirely comparable. Still, since we expect this potential overestimation to be the same in all the patients; we find it is acceptable to correlate the muscle atrophy found on MRI to the reduced lean mass found by DXA scan. According to our knowledge this study is the first to report reduced muscle mass surrounding the hip joint when comparing HRA to THA implants. We found that a DXA examination provides a low-cost alternative to the MRI when evaluating the muscle tissues around the hip implant, since the precision when applying the regions of interest was acceptable.

Changes in bone tissue, implant position and range of motion

HRA is marketed for young and active patients and should restore the anatomy of the hip joint and result in a better range of motion (ROM). In study IV, we found the adduction as well as the internal and external rotation of the hip joint to be significantly decreased in HRA hips compared to THA hips. Our findings are supported by experimental studies which have demonstrated that HRA has a decreased range of motion compared to THA (84;100), primarily due to impingement.

By contrast, clinical studies have demonstrated an equal range of motion comparing HRA and THA implants (68;105;183). Also, studies have demonstrated that an acetabular cup inclination above 50˚ is associated with excessive rim wear and increased metal wear (48;77). The cup inclination in the ReCap patients (study IV) was between 59-85˚ which is higher than recommended by the manufacturer (anteversion 10-15˚ and cup inclination 40-45˚). However, the cup position was not different in comparison with the MHE group and there were no implant dislocations. Also, the cup anteversion was acceptable in both groups.

Looking at the femoral stem in the ReCap group, we found eight patients with the femoral stem not located in the center of the femoral neck seen on the lateral projection on the radiographs. In four patients the femoral stem was positioned anteriorly and in four patients the femoral stem located posteriorly. Furthermore, in 17 out of 19 patients, we found smaller alterations of the bone tissue in the anterior or posterior part of the cortical bone in the femoral neck. These changes in the bone tissue could possibly be caused by a synovial reaction due to accumulation of metal wear debris. Also, if the implant is not positioned correctly, there is a risk of impingement between the femoral neck and the acetabular cup, which could possibly lead to decreased range of motion.

Within recent years the Australian registry (AONNJR) and Danish national orthopedic association (3;4), among others, have emphasized the need for a meticulous selection of the possible candidates to receive a HRA implant. Earlier a wider selection of patients was offered this type of implant without taking into

account the effect of poor bone quality in the femoral head and neck, osteonecrosis or larger cysts in the femoral head and neck, small head sizes and finally, the learning curve of the surgeon. These different causes may have contributed to the higher revision rate seen in HRA compared to a cementless THA, which, in Denmark, would have been the alternative choice of treatment in these patients. Furthermore, the recall from the market of the ASR implant, due to high failure rates, could possibly reduce the overall failure rate in HRA implants. Aseptic loosening is still an important factor in failure of HRA implants despite the intended wear resistant MOM articulation and finally, the possible, negative side-effects of MOM wear debris on the bone and soft tissues surrounding the implants remain unclear. If all these considerations and reservations are taken into account the future outcome of HRA may be comparable to THA. Until then, further follow-up on HRA implants is needed and the side-effects of MOM wear particles and the possible connection to elevated failure rates in HRA and MOM THA implants needs further meticulous investigation and follow-up.

Discussion of the methods

Study I

The meta-analysis in our study is limited by 1) the small number of studies which we registered and included in the meta-analysis when comparing HRA to THA, 2) the analyses were based on a heterogeneous group of studies and the inclusion criteria were not standardized, and 3) one study was a randomized clinical trial whereas the remaining studies were observational. The estimated inter-study variance in our meta-analysis was not statistically significant. In spite of the fact that the number of studies included in the meta-analysis is small, we have performed a random effect model analysis. Interpretation of the results must therefore be performed cautiously since the estimated between study variance will have a poorer precision (32).

Also, the possible effect of a publication bias is not known in our study. This type of bias is well known in all research since negative research results are less likely to be published and published studies are more likely to have higher impact than unpublished studies. The results from the meta-analysis show a higher risk ratio in HRA implants compared to cementless THA implants, however, more large-scale randomized clinical trials are needed in order to be able to perform a meta-analysis consisting of a greater number of studies and preferably more homogeneous studies to be able to make a stronger conclusion of the results.

Study II

Microdialysis - recovery of metabolites and baseline measurements

One limitation in study II is the lack of a recovery determination and the lack of a baseline measurement of the metabolites. The relative recovery (RR) of a particular substance when performing microdialysis is defined as the concentration in the dialysate expressed as a percent of the concentration in the interstitial fluid (179). The RR of the four metabolites in our study was unknown as we did not perform a RR determination before, during or after the surgery. This is due to the fact that it was not technically possible to place the microdialysis catheter in the bone canal and perform the microdialysis before the hip joint was opened. Also, as we did not start the microdialysis till after the surgery had ended, we did not achieve any baseline measurement of the four metabolites. However, all patients underwent surgery during the same conditions such as operating room temperature; supine positioning during surgery, the cementation process of the femoral component and all but one patient received spinal anesthesia with propofol sedation. Furthermore, the preparation of the bone canal was equal in all patients, leaving the same size of dead space around all catheters and likewise the possible blood clot formation in the bone canal would be of equal proportions. Finally, all of the microdialysis catheters had the same membrane length and qualities. Therefore, we find it is acceptable to assume that the recovery is the same in all the patients and that the results obtained by the microdialysis are therefore comparable between the groups.

In the study we found that the microdialysis catheters were displaced in 11 patients with the majority of the displacements seen in the in the Post group (seven patients of the 11). This is a possible selection bias in the study. We do not have any valid measurements in the patients with displaced microdialysis catheters and since the

majority of displacements occurred in the group operated by the posterior surgical approach this could possibly have influenced the final results if the data from the displaced patients were very different from the mean results seen in the randomization groups.

Laser Doppler flowmetry in the femoral head and neck

In study II, we found no difference between the groups regarding the blood flow measurements. However, significant differences in blood flow measurements between the posterior and the antero-lateral surgical approach have been demonstrated by Amarasekera et al, Khan et al, and Steffen et al (7;95;163). This inconsistency is most probably due to the fact that our first measurement was not performed until after the joint-capsule was opened. It was not technically possible to perform a blood flow measurement before the joint capsule was opened. Also, we measured the perfusion in only a small area in the upper quadrant of the junction between the femoral head and neck. A measurement of a greater area or at several different positions in the femoral head and neck could have strengthened our study, but doing so was clinically not feasible.

PET scan studies by Ullmark et al (177;178) have showed that a decrease of metabolism resulting in osteonecrosis involves a greater area of the femoral head and neck. Vascular studies by Beaulé et al and Gautier et al (18;65) have demonstrated the medial circumflex artery is the main blood supply to the entire femoral head and neck in the majority of patients. Based on these findings, we find it acceptable to assume that the measurements in the upper quadrant of the femoral head and neck are representative of the total femoral head and neck. Laser Doppler flowmetry measurements show very large variations during measurements and the probes used in the measurements are very sensitive to stir. Therefore the method should be considered to be used in the assessment of whether there is a pulsatile blood flow in the tissue as opposed to be used to assess absolute values in terms of tissue perfusion.

Study III

The femoral component of the HRA is a y-symmetrical implant with a very short and narrow centralizer. This can lead to problems visualizing the tantalum markers on the stem with the marker-based RSA analysis. The tantalum markers are attached to the tip of three towers which again is attached to the centralizer of the femoral component. In our study a total of six patients were excluded due to occluded tantalum markers when using the marker-based RSA method. Therefore there is a risk of type 2 error in this study due to a lack of patients with acceptable measurements. On the contrary, CAD models can be more difficult to fit to the radiographic projection of the implant due to the large diameter of the metal head, which is partially occluded by the acetabular metal shell in clinical patients. Still, all the patients with occluded implant markers and problematic marker-based analysis (n=6) could be analyzed using the CAD model-based method.

The size of the ReCap implant is small and the majority of the surface articulates with the shell, and for this reason it can be difficult to obtain sufficient implant marker dispersion for marker-based RSA. On the contrary, the CAD model is more clinically representative in terms of shape and size as compared with the small marker-based

model created from the tantalum markers attached to the centralizer. For this particular implant shape, CAD-models may therefore represent a more clinically relevant assessment of the mean implant migration than the marker-based analysis.
One reason that the marker-based RSA method demonstrated less precision in the clinical study probably relates to the relatively close-placement of only three markers on the implant-centralizer resulting in a higher than standard condition number (68) as compared with marker-based analysis of standard femoral stems. The condition number for standard femoral stems is typically low, since it is possible to have a much larger geometrical spread of the implant markers than with the ReCap implant investigated in the present study. It was not possible to spread the markers further on the centralizer and concurrently avoid marker-occlusion by the cap, and neither was it possible to place markers elsewhere on the implant, i.e. on the edge of the cap, as they would have resulted in abrasive metal-wear.
Maximum Total Point Motion (MTPM) is a measure of (unsigned) absolute migration for the implant, which is normally used in marker-based RSA, but is given by the model-based RSA software for migration analysis by both RSA methods that we utilized. For marker-based analysis MTPM can be related to one of three points (implant markers) that migrated the most (152), yet for model-based RSA it relates to one in approximately 3000 points (in the CAD model) that migrated the most and does not provide a similar simple and comparable estimate for maximal translatory migration between the investigated patients. For easier comparison the total translation (TT) and total rotation (TR) may be calculated by use of the Pythagorean Theorem and it has been used in former publications (91;167). When the signed translations and rotations are published TT and TR may easily be calculated for comparison between studies.

Study IV

MRI scans of soft tissue lesions
The MRI scans have only been assessed by one experienced radiologist. This should optimally have been performed by two independent radiologists to avoid misinterpretations. Furthermore, the field of diagnosing soft tissue lesions on MRI is new and the risk of misinterpretation is therefore present. Also, there is a need for standardized classification systems as this does not currently exist. There has been proposal for guidelines when evaluating the lesions in soft tissues surrounding MOM implants (13), but so far none are widely used. This increases the risk of misinterpretation and can make it difficult to compare the results from our study with other studies. In the patients with diagnosed soft tissue lesions, we did not obtain any biopsy, which is why we have not been able to assess the soft tissue lesions further in terms of histological diagnosis and a possible correlation to ALVAL.

DXA
The results from the BMD measurements on the femoral neck showed an acceptable precision. A standardized set-up was used and the precision in the double examination BMD assessment in the seven Gruen zones varied from 0.77-3.82 (CV%) in the ReCap group and 0.99-2.17 (CV%) in the MHE group. These findings correspond with other studies reporting a CV% between 1-5 % on HRA as well as

THA. These studies also reported that measurement of the peri-prosthetic BMD around resurfacing implants is very susceptible to leg-rotations between follow-up examinations due to the small size of the zones (25;39;102;127;137).
We did not encounter rotation problems since the leg was positioned with the leg in 20° internal rotation and the foot fixed on a triangular positioner at all scans. We performed two customized regions of interest on the total body scan to assess the muscle and fat mass. As we only had one total body scan at the five-year follow-up, we assessed the intra-observer variation for placing the customized regions for assessment of the local hip fat and muscle in the total body scan and found that the intra-observer variation was small (CV between 1-5%). Therefore, the method should be applicable for any region of interest in total body scan, and also for prospective follow-up, provided that the scanner software supports creation of custom-designed regions and that standardized reference points are established in order to obtain a correct placement of the region of interest.

Radiographs
The radiographs have only been reviewed once by an experienced orthopedic surgeon. Preferably this should have been performed by at least two independent and experienced surgeons or radiologists. The review of the radiographs for assessment of possible radiolucency lines and osteolysis in the DeLee and Gruen zones was performed by viewing the radiographs and determining which of the defined DeLee and Gruen zones were involved, but no quantification of lesion size was applied as this is difficult in both area and depth.

Clinical evaluation
The Oxford Hip Score, the visual analogue score and an evaluation of the patients' satisfaction were completed by the patients themselves, whereas the Harris Hip Score was completed by the orthopedic surgeon. The study is limited as the RCT was not blinded, and both the patients and the orthopedic surgeon were informed of which type of implant had been inserted.

Generalizability

Study I
The results from the meta-analysis indicating a higher risk of failure in HRA compared to cementless THA may be used for decision making of the type of implant a patient should be offered. However, more research including large-scale randomized clinical trials is needed to be able to make better judgements for the patient-group with the greatest benefit of the treatment.

Study II
Our results showed ischemia in the femoral head and neck using both the posterior and the antero-lateral surgical approach. This ischemia may be part of the explanation for the development of osteonecrosis in the femoral head and neck. However, other possible mechanisms resulting in vascular injuries such as heating during the curing process of the bone cement and the surgical technique applied to the bone still needs further investigation.

Study III
The design of the resurfacing implant is supposed to restore the anatomy of the hip joint and our results showed that the ReCap implants were stable at a five-year follow-up. Further follow-up in the coming years will be needed in order to see if the ReCap implants remain stable at longer term and if the fixation or implant migration differs from other HRA brands. CAD model-based RSA should be repeatable in any institution whereas marker-based RSA would depend on similar positions of the implant markers.

Study IV
The results showed that HRA implants restores the anatomy of the hip joint and preserves the bone mineral density of the femoral head and neck. However, soft tissue lesions surrounding the HRA implants was more frequent compared to THA. We suggest that further investigation is conducted in order to assess these lesions, since this may be important regarding the survival of the HRA implants. The results from the MRI scan and the assessment of osteolysis on the radiographs are limited by the fact that only one observer assessed the pictures. Also, in the assessment of muscle and fat mass by DXA scan, the results may depend on the type of DXA scanner available. The results may therefore vary in accordance with this.

8. Conclusion

Study I
The study showed an increased revision rate in HRA compared to THA. Aseptic loosening, femoral neck facture, and necrosis of the femoral head are the main complications that lead to implant failure and inferior survival of this implant. Proper patient selection and further investigation into potential adverse effects from MOM wear particles still need to be clarified and will have the potential to lower the risk of femoral head. Our results were based on a small group of studies, and further investigation consisting of large-scale randomized clinical trials comparing HRA to THA is needed to identify the best treatment for young patients suffering from end stage OA.

Study II
The microdialysis study was used to continuously monitor the metabolism in human bone tissue though it did not show that a specific surgical approach results in absolute ischemia. HRA using the posterior surgical approach leads to increased ischemia in the femoral head and neck, which could be explained by a decrease in perfusion initiated at surgery. Still, the antero-lateral surgical approach also results in considerable ischemia and other possible explanations such as damage to the retinacular vessels during the surgical preparation or altered microcirculation caused by heating from the cementation process and these subjects need further investigation.

Study III
The marker-based RSA method is more precise compared with model-based RSA utilizing CAD and RE models; however both methods are more precise then the detection threshold for detection of loose implants found by Kärrholm et al and Ryd et al (93;147). We validated that marker-based RSA may detect changes in mean TT above 0.5 mm, and model-based RSA may detect changes in mean TT above 1 mm within a group. Clinically CAD-models may better describe the anatomical signed implant migrations compared with the small marker-model in the ReCap implant. Considering the slightly poorer precision of CAD model-based RSA a slightly larger sample size should be aimed at with CAD model-based RSA, however, as small marker-models result in problems visualizing the tantalum markers on the femoral centralizer the sample size difference to maintain power may not be that diverging after all. We find CAD model-based RSA to be a clinically acceptable and potentially better alternative to marker-based RSA in HRA. Clinically we found the ReCap hip resurfacing implant in this study to be stable at a 5 years follow-up with mean translatory (TT) migration measurements throughout the observation period that were within the precision limits of the measurement methods. Therefore we could not conclude any motion of the ReCap implant throughout follow-up.

Study IV
HRA implants provide a good patient reported outcome and restores the physiologic load on the femoral bone by preserving the BMD in the femoral neck. Also, the muscle mass surrounding the hip was better preserved in HRA patients as

demonstrated by a new methodology in DXA scans. However, HRA is associated with decreased ROM and it seems of great importance that the component is inserted correctly in order to avoid impingement. Also, the formations of soft tissue lesions which is likely to be related to metal wear-debris remain unanswered. Further investigation into the possible side-effects of metal wear-debris is necessary to clarify the origin of soft tissue lesions and follow-up on all patients with MOM implants should be considered.

Since the soft tissue lesions in our study were far more common in MOM implants compared to MOP implants further investigation of the basic causes of these lesions must be performed. Till then regular follow-up on patients with MOM implants is advised. MRI with special metal-artifact removal sequences or examination at low Tesla is one option to monitor and evaluate the peri-prosthetic soft tissues. Further investigations including assessment of metal-ion blood concentrations levels as a direct result of metal wear-debris as well as potential allergic or toxic reactions to metal wear-debris is another option of monitoration of unwanted negative side-effects in MOM implants.

9. Perspectives and future research

Study I
Future reviews and meta-analysis should preferably be based on high scale randomized clinical trials in order to be able to compare the studies and make stronger conclusions. Single series following up on HRA implants as well as randomized clinical trials is of greatest importance.

Study II
In study II a continued follow-up on the 38 patients will be performed in order to be able to assess if any complication that might occur can be correlated to the results from the blood flow measurements and the microdialysis. If a femoral neck fracture or an avascular necrosis occurs, it would be of great interest to investigate if this could be correlated to the values obtained from the microdialysis analysis to see if the possible fractures or avascular necrosis could be correlated to the patients with the most pronounced ischemic changes or per-operative blood flow changes. Also a follow-up in these patients with a PET scan 2-4 years after surgery could be of interest to assess any areas of avascular osteonecrosis. Other possible perspectives of micodialyis in orthopaedics could be investigation into the physiological bone metabolism as well as metabolism bone metabolism in standard orthopaedic procedures. Laser Doppler flowmetry could be used in order to assess if there is a pulsatile blood flow or not in areas which potentially could be interrupted of blood supply e.g. during surgical procedures or not in areas with potential.

Study III
CAD model-based RSA has been validated for the clinical use in HRA implants and this can be used in future studies. Since problems with occluded markers were seen in a greater proportion in marker-based RSA, leading to drop out of the analysis, this can be overcome using CAD model-based RSA since all the CAD model-based analysis could be performed and no radiographs had to be left out of the analysis. CAD model-based RSA is less precise, however, sample size calculations have predicted only a few more patients in each group compared to marker-based RSA sample size calculations.

Study IV
BMD was preserved and in some parts of the femoral neck even increased in HRA implants. Further long term follow-up is interesting in order to see if this BMD can be correlated to long term implant survival or fewer complications in terms of fractures or avascular necrosis. It will be of greatest to see a 10 year follow up to be able to compare with THA at long term follow-up. Regarding the possible effects of MOM wear-particles on the soft tissues and whole body, the patients will be further be examined by blood tests and skin patch tests to investigate a possible link between an allergic reaction and the soft tissue lesions demonstrated on the MRI scan.
This could be supplemented by biopsies from the soft tissue lesions and a long-term follow-up to see if the patient satisfaction continues.

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Appendices

PhD and Doctoral Theses from the Orthopaedic Research Group, www.OrthoResearch.dk, University Hospital of Aarhus, Denmark

PhD Theses

In vivo and vitro stimulation of bone formation with local growth factors
Martin Lind, January 1996
www.OrthoResearch.dk

Gene delivery to articular cartilage
Michael Ulrich-Vinther, September 2002
www.OrthoResearch.dk

The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles
Ole Rahbek, October 2002
www.OrthoResearch.dk

Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques
Søren Kold, January 2003
www.OrthoResearch.dk

Stimulation and substitution of bone allograft around non-cemented implants
Thomas Bo Jensen, October 2003
www.OrthoResearch.dk

The influence of RGD peptide surface modification on the fixation of orthopaedic implants
Brian Elmengaard, December 2004
www.OrthoResearch.dk

Biological response to wear debris after total hip arthroplasty using different bearing materials
Marianne Nygaard, June 2005
www.OrthoResearch.dk

DEXA-scanning in description of bone remodeling and osteolysis around cementless acetabular cups
Mogens Berg Laursen, November 2005
www.OrthoResearch.dk

Studies based on the Danish Hip Arthroplasty Registry
Alma B. Pedersen, 2006

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Reaming procedure and migration of the uncemented acetabular component in total hip replacement
Thomas Baad-Hansen, February 2007
www.OrthoResearch.dk

On the longevity of cemented hip prosthesis and the influence on implant design
Mette Ørskov Sjøland, April 2007
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Combination of TGF-β1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-structures in vivo
Anders Lamberg, June 2007
www.OrthoResearch.dk

Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration
Inger Mechlenburg, August 2007
Acta Orthopaedica (Suppl 329) 2008;79

Rehabilitation of patients aged over 65 years after total hip replacement - based on patients' health status
Britta Hørdam, February 2008
www.OrthoResearch.dk

Efficacy, effectiveness, and efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty
Kristian Larsen, May 2008
www.OrthoResearch.dk

Rehabilitation outcome after total hip replacement; prospective randomized studies evaluating two different postoperative regimes and two different types of implants
Mette Krintel Petersen, June 2008
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CoCrMo alloy, *in vitro* and *in vivo* studies
Stig Storgaard Jakobsen, June 2008
www.OrthoResearch.dk

Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants. Stereological methods and experiments in dogs
Jørgen Baas, July 2008
Acta Orthopaedica (Suppl 330) 2008;79

The Influence of Local Bisphosphonate Treatment on Implant Fixation

Thomas Vestergaard Jakobsen, December 2008
www.OrthoResearch.dk

Surgical Advances in Periacetabular Osteotomy for Treatment of Hip Dysplasia in Adults
Anders Troelsen, March 2009
Acta Orthopaedica (Suppl 332) 2009;80

Polyethylene Wear Analysis. Experimental and Clinical Studies in Total Hip Arthroplasty.
Maiken Stilling, June 2009
Acta Orthopaedica (Suppl 337) 2009;80

Step-by-step development of a novel orthopaedic biomaterial: A nanotechnological approach.
Thomas H.L. Jensen, September 2009
www.OrthoResearch.dk

Osteoclastic bone resorption in chronic osteomyelitis
Kirill Gromov, November 2009
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Use of medications and the risk of revision after primary total hip arthroplasty
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Different fixation methods in anterior cruciate ligament reconstruction
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A comparison of two types of osteosynthesis for distal radius fractures using validated Danish outcome measures
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The influence of parathyroid hormone treatment on implant fixation
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Strontium in the bone-implant interface
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Gene transfer for bone healing using immobilized freeze-dried adeno-associated viral vectors
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Mobile or fixed bearing articulation in TKA? A randomized evaluation of gait analysis, implant migration, and bone mineral density, December 2011
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Doctoral Theses

Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs
Kjeld Søballe, 1993
Acta Orthop Scand (Suppl 255) 1993;54

Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation
Martin Lind, October 1998
Acta Orthop Scand (Suppl 283) 1998;69

Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods
Søren Overgaard, 2000
Acta Orthop Scand (Suppl 297) 2000;71

Adult hip dysplasia and osteoarthritis. Studies in radiology and clinical epidemiology
Steffen Jacobsen, December 2006
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Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing
Michael Ulrich-Vinther, March 2007
Acta Orthopaedica (Suppl 325) 2007;78