Karolinska Institutet, Institutionen för kliniska vetenskaper,
Danderyds sjukhus, Enheten för ortopedi
Stockholm 2013

UNCEMENTED HIP ARTHROPLASTY IN PRIMARY AND REVISION SURGERY

Patterns of bone remodelling and options to influence periprosthetic bone loss

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i aulan, Danderyds sjukhus,

Fredagen den 13 december 2013, kl 09.00
av Mats Salemyr

HUVUDHANDLEDARE:
Prof. André Stark
Karolinska Institutet
Institutionen för kliniska vetenskaper,
Danderyds Sjukhus,
Enheten för ortopedi

BIHANDLEDARE:
Doc. Torbjörn Ahl

Olof Sköldenberg, MD, PhD

Olle Muren, MD, PhD

Alla vid,
Karolinska Institutet
Institutionen för kliniska vetenskaper,
Danderyds Sjukhus,
Enheten för ortopedi

FAKULTETSOPPONENT:
Prof. Hans Mallmin
Uppsala universitet
Institutionen för kirurgiska vetenskaper,
Enheten för ortopedi

BETYGSNÄMND:
Doc. Torkel Brismar
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik
Enheten för medicinsk bild, funktion
och teknik

Prof. Kjell G Nilsson
Umeå universitet
Kirurgisk och perioperativ vetenskap
Enheten för ortopedi

Doc. Gunnar Flivik
Lunds universitet
Medicinska fakulteten
Enheten för ortopedi

ABSTRACT

Introduction

The incidence of hip arthroplasty surgery in young and active patients is increasing. Consequently, an increasing number of patients will live with hip prostheses for longer periods of time in the future. The mismatch in modulus of elasticity between the stiffer metal components and the surrounding bone will induce periprosthetic adaptive bone remodelling. The clinical importance of this is still uncertain but the risk of late occuring complications, secondary to periprosthetic bone loss, should not be neglected.

This thesis focuses on patterns of bone remodelling around uncemented hip implants and on options how to influence the bone remodelling process.

Hypotheses

We hypothesized that (1) femoral hip revision surgery with a proximally coated uncemented tapered stem is a reliable procedure, with good results, if bone defects at revision are moderate, (2) the femoral adaptive periprosthetic bone remodelling is pronounced after such an operation, (3) oral bisphosphonates, once weekly for six months, will reduce the periprosthetic bone resorption around an uncemented tapered stem up to 2 years after primary hip arthroplasty, (4) an ultra-short wedge shaped uncemented femoral stem gives less periprosthetic bone loss than a conventional uncemented tapered stem, and finally, (5) an acetabular component with a backside coating of a three-dimensional porous titanium construct gives less periprosthetic bone loss than a conventional porous- and hydroxyapatite coated titanium acetabular shell.

Materials and methods

Two different hydroxyapatite coated femoral stems and two titanium acetabular cups, with differing properties regarding shell backside coating and articulating polyethylene, were evaluated.

Bone mineral density (BMD) was measured with Dual Energy X-ray Absorptiometry (DEXA). Radiographic assessment was done with consecutive radiographs in study I-III. Implant migration was measured with Einzel-Bild-Röntgen-Analyse (EBRA) in study III and with radiostereometric analysis (RSA) in study IV-V. RSA was also used to analyze polyethylene wear in study V. Clinical outcome was evaluated with self administered score protocols.

Results

Study I: A retrospective analysis of 60 patients (62 hips), with a mean follow-up of 6 years after uncemented femoral revision due to aseptic loosening, with moderate bone loss at revision, revealed a stem survival rate of 95%. Radiographical signs of stem osseointegration, as well as diminishing peri-implant osteolysis, were recorded.

Study II: In a cross sectional study 22 patients from the cohort in study I, with a healthy hip on the contralateral side, were evaluated with DEXA after a mean follow-up of 6 years. We noted a large reduction of 36-45% in BMD in Gruen zones 1-2 and 6-7 compared to the contralateral hip.

Study III: In a randomized, double-blind, placebo-controlled trial of 73 patients operated with an uncemented stem due to primary osteoarthritis, the treatment group was given risedronate once weekly for 6 months. In the treatment group BMD loss in the proximal femur was reduced with 7% 12 months after surgery but no statistically significant reduction was found after 2 years.

Study IV: In a randomized controlled trial of 51 patients periprosthetic bone remodelling was evaluated around an ultra short stem, compared to a conventional tapered stem, in uncemented THA due to primary osteoarthritis. BMD loss was significantly reduced around the ultra short stem up to 2 years after surgery.

Study V: In a randomized controlled trial of 51 patients, comparing two acetabular implants with differing properties regarding shell backside coating and articulating polyethylene, no differences in periprosthetic bone remodelling, implant fixation or polyethylene liner wear was found, up to 2 years after surgery.

Conclusions

Adaptive periprosthetic bone remodelling after uncemented total hip arthroplasty could be reduced with bisphosphonates and with altered stem design. Periacetabular bone demineralization could not be reduced with a new porous titanium construct material. Alpha-tocopherol diffusion of HXLPE liners gave reduced creep but not less polyethylene wear up to 2 years after surgery.

An uncemented, proximally porous- and HA-coated tapered stem could be used with good results in femoral revision surgery if bone loss was moderate. Even though stem fixation was excellent, proximal femoral bone demineralization was pronounced.

From
DEPARTMENT OF CLINICAL SCIENCES, DANDERYD HOSPITAL
Karolinska Institutet, Stockholm, Sweden

UNCEMENTED HIP ARTHROPLASTY IN PRIMARY AND REVISION SURGERY

PATTERNS OF BONE REMODELLING AND OPTIONS TO INFLUENCE PERIPROSTHETIC BONE LOSS

Mats Salemyr

Karolinska Institutet

Stockholm 2013

Published by Karolinska Institutet.
Art direction & production by Robert Szczypinski,
www.shipy.com.

Printed by Linköpings Tryckeriaktiebolag AB.
www.ltab.se

ISBN 978-91-7549-360-2

For Jenny, Filip, Jakob and Sara

Abstract

ABSTRACT

Introduction

The main reason for failure in total hip arthroplasty (THA) is aseptic loosening of the components. In younger and more active patients biological fixation with uncemented implants has shown better outcome than cemented fixation (1). Even though long term fixation is improved the mismatch in modulus of elasticity between the stiffer metal components and the surrounding bone will induce periprosthetic adaptive bone remodelling (2, 3). The incidence of hip arthroplasty surgery in young and active patients is increasing and consequently an increasing number of patients will live with hip prostheses for longer periods of time. The clinical importance of the ongoing adaptive bone remodelling is still uncertain but the risk of late complications secondary to periprosthetic bone loss should not be neglected.

This thesis focuses on patterns of bone remodelling around uncemented hip implants and options of how to influence the bone remodelling process.

Hypotheses

We hypothesized that (1) femoral hip revision surgery with a proximally coated uncemented tapered stem is a reliable procedure if bone defects prior to revision are moderate, (2) the femoral adaptive periprosthetic bone remodelling is pronounced after such an operation, (3) oral bisphosphonates, once weekly for six months, will reduce the periprosthetic bone resorption around a proximally coated uncemented tapered stem up to 2 years after primary hip arthroplasty, (4) an ultra-short wedge shaped uncemented femoral stem induces less periprosthetic bone loss than a conventional uncemented tapered stem and finally (5) an acetabular component with a backside coating of three-dimensional titanium porous construct induces less periprosthetic bone loss than a conventional porous- and hydroxyapatite coated titanium acetabular shell.

Materials and Methods

Two different hydroxyapatite coated femoral stems and two titanium acetabular cups, with differing properties regarding shell backside coating and articulating polyethylene, were evaluated.

Bone mineral density (BMD) was measured with Dual Energy X-ray Absorptiometry (DEXA). Radiographic assessment was done with consecutive radiographs in study I-III. Implant migration was measured with Einzel-Bild-Röntgen-Analyse (EBRA) in study III. Radiostereometric analysis (RSA) was used to measure implant migration in study IV-V and polyethylene wear in study V.

Clinical outcome was evaluated with self administered score protocols.

Abstract

Results

STUDY I

A retrospective analysis of 60 patients (62 hips), with a mean follow-up of 6 years after uncemented femoral revision due to aseptic loosening, with moderate bone loss at revision, revealed a stem survival rate of 95%. Four hips required re-revision due to fracture or dislocation. No stem was loose. Radiographical signs of stem osseointegration, as well as, diminishing peri-implant osteolysis were recorded.

STUDY II

In a cross sectional study 22 patients with a healthy hip on the opposite side, from the cohort in study I, were evaluated with DEXA after a mean follow-up of six years. We noted a large reduction of 36-45% in BMD in Gruen zones 1-2 and 6-7, compared to the contralateral hip.

STUDY III

In a randomized, double-blind, placebo-controlled trial of 73 patients operated with an uncemented stem due to primary osteoarthritis, the treatment group was given risedronate once weekly for 6 months. In the treatment group BMD loss in the proximal femur was reduced with 7% 12 months after surgery but no statistically significant reduction was found after 2 years.

STUDY IV

In a randomized controlled trial of 51 patients periprosthetic bone remodelling was evaluated around an ultra short stem compared to a conventional tapered stem in uncemented THA due to primary osteoarthritis. BMD loss was significantly reduced around the ultra short stem.

STUDY V

In a randomized controlled trial of 51 patients, comparing two acetabular implants with differing properties regarding shell backside coating and articulating polyethylene, no differences in periprosthetic bone remodelling, implant fixation or polyethylene liner wear was found, up to 2 years after surgery.

Conclusions

Adaptive periprosthetic bone remodelling after uncemented total hip arthroplasty could be reduced pharmacologically with bisphosphonates and with altered stem design. Periacetabular bone demineralization could not be reduced with a new porous titanium construct material with enhanced porosity. Alpha-tocopherol diffusion of HXLPE liners gave reduced creep but not less polyethylene wear up to 2 years after surgery.

An uncemented, proximally porous- and HA-coated tapered stem could be used with reliable results in femoral revision surgery if bone loss at revision was moderate. Even though stem fixation was excellent, proximal femoral bone demineralization was pronounced.

List of papers

LIST OF PAPERS

I. Good results with an uncemented proximally HA-coated stem in hip revision surgery:
62 hips followed for 2-13 years.

Mats Salemyr, Olof Sköldenberg, Henrik Bodén, Torbjörn Ahl, Per Adolphsson
Acta Orthopaedica 2008;79 (2): 184-193

II. Large femoral bone loss after hip revision using the uncemented proximally porous-coated Bi-Metric prosthesis:
22 hips followed for a mean of 6 years.

Per Adolphsson, Mats Salemyr, Olof Sköldenberg, Henrik Bodén
Acta Orthopaedica 2009;80 (1): 14-19

III. The effect of weekly Risedronate on Periprosthetic Bone Resorption Following Total Hip Arthroplasty.
A randomized, double-blind, placebo-controlled trial.

Olof Sköldenberg, Mats Salemyr, Henrik Bodén, Torbjörn Ahl, Per Adolphson
Journal of Bone and Joint Surgery Am. 2011;93:1857-64

IV. Ultra-short stem compared to conventional tapered stem in uncemented total hip arthroplasty.
A randomized controlled trial of femoral periprosthetic bone remodelling and stem fixation.

Mats Salemyr, Olle Muren, Henrik Bodén, Torbjörn Ahl, Thomas Eisler, André Stark, Olof Sköldenberg
In manuscript

V. Porous titanium construct cup with alfa-tocopherol diffused polyethyelene liner compared to conventional cup and polyethylene liner in uncemented total hip arthroplasty.
A randomized controlled trial of periacetabular bone remodelling, cup fixation and polyethylene liner wear.

Mats Salemyr, Olle Muren, Henrik Bodén, Torbjörn Ahl, Ghazi Chammout, André Stark, Olof Sköldenberg
In manuscript

The papers in this thesis will be referred to in the text with their Roman numerals (Study I-V).

Contents

CONTENTS

Abbreviations

1 ABBREVIATIONS

3D	Three dimensional
ASA	American Society of Anesthesiologists
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CN	Condition number
CoCr	Cobalt-Chrome
CV	Coefficient of variation
DEXA	Dual-Energy X-ray Absorptiometry
EBRA	Einzel-Bild-Röntgen-Analyse
EQ-5D	European Quality of Life-5 Dimensions
HA	Hydroxyapatite
HHS	Harris Hip Score
HXLPE	Highly cross-linked polyethylene
ME	Mean error of rigid body fitting
NARA	Nordic Arthroplasty Register Association
OA	Ostheoarthritis
PMMA	Polymethylmethacrylate
RCT	Randomized controlled trial
ROI	Region of interest
RSA	Radiostereometric analysis, radiostereometry
SD	Standard deviation
SHAR	Swedish Hip Arthroplasty Register
THA	Total hip arthroplasty
Ti	Titanium
Ti-6Al-4V	Titanium-6Aluminium-4Vanadium
UHMWPE	Ultra high molecular weight polyethylene
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

2 DEFINITIONS

ADAPTIVE BONE REMODELLING
Dynamic changes in bone mineral content due to different loading conditions over time.

ASEPTIC LOOSENING
Mechanical loosening of a prosthesis component without signs of infection.

BONE INGROWTH
New bone formation in direct contact with the porous structured surface of an implant.

BONE LOSS
Diminishing bone mass either because of osteolysis or bone resorption.

BONE REMODELLING
Adaptive changes in bone architecture. See also adaptive bone remodelling.

CREEP
Plastic deformation of material, in this thesis of polyethylene, without production of wear debris.

CORTICAL HYPERTROPHY
Increased cortical bone mass secondary to increased load.

DISUSE ATROPHY
Bone mineral decrease due to off-loading of bone. See also stress shielding.

HYDROXYAPATITE
Calcium phosphate mineral. The principal inorganic constituent of bone.

IMPLANT
A medical device made from biomaterials, intentionally placed in the body.

OSSEOINTEGRATION
Direct structural and functional connection between living bone and the surface of a load-bearing implant.

MODULUS OF ELASTICITY
The ratio between stress per unit area and the resulting deformation.

OSTEOLYSIS
Localized areas of active bone dissolution or resorption in relation to a joint prosthesis. Often caused by wear particles from the joint

PEDESTAL SIGN
Endosteal bone formation at the tip of a femoral stem.

POROUS COATING
Coating of an implant deliberately applied to contain void regions with the intent of enhancing fixation of an endoprosthesis

PRESS FIT
Insertion of an implant into an undersized pre made cavity.

RADIOLUCENT LINES
Linear radiolucencies lining the implant contour without densifications.

REACTIVE LINES
Endosteal densifications parallel to and in close proximity to the contour of an implant.

RIGID BODY
In RSA, the number of markers forming a segment corresponding to either part of the body or the object of interest

SPOT WELDS
Thin endosteal bone formation bridging from the cortical bone to an implant´s surface

STRESS SHIELDING
Non-anatomical reduction in bone mineral density as a result of off-loading bone by an implant.

UNCEMENTED
Implants designed for fixation by bone ingrowth.

WEAR
Undesired removal of material from implants and other biomaterials.

WOLFF´S LAW
States that bone will remodel in response to the load it is placed under. Less load will decrease and more load will increase bone mass.

Introduction

3 INTRODUCTION

Background

Total hip arthroplasty (THA) is one of the best treatment procedures that health care systems in the developed world can provide from a gain in life-quality perspective. Pain from degenerative, as well as, traumatic hip disorders is effectively treated with a joint replacement. The incidence of hip replacement has increased continuously over the last few decades worldwide. Today, 16 000 THAs are performed annually in Sweden (1) and 1.5 – 2 million globally.

Component fixation in total hip arthroplasty

The modern era of THA started in the 1960s with the Charnley prosthesis. Component fixation was achieved with the use "bone cement", polymethylmethacrylate (PMMA). This plastic polymer is not a glue but a grout where fixation relies on microinterlock from cement intrusion into the porosity of cancellous, trabecular bone. Cement for component fixation is still used extensively in the Nordic countries and the outcome has been excellent. The 10-year prosthesis survival rate for cemented implants in Sweden was 95.2% in 2011, (Table 1).

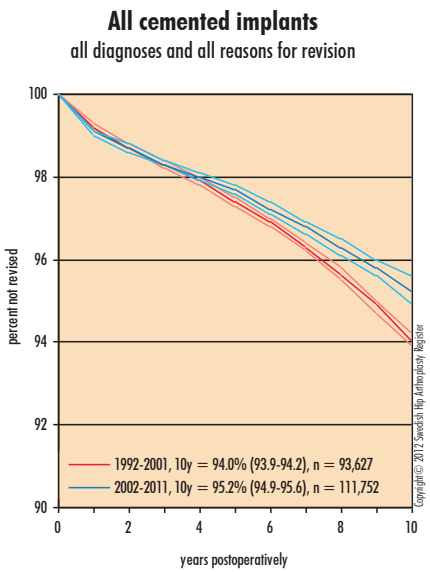


TABLE 1. *Reprinted with permission from the Swedish Hip Arthroplasty Register (SHAR).*

As a consequence of the excellent results the indications for THA-surgery have widened. Younger and more active patients are now undergoing THA. These patients will live with their hip replacements for longer periods of time and as a consequence of a more active life style, the functional performance of the new hip joint will have to have to meet greater challenges. In this group of patients, the cemented interface between bone and the implant has limitations in its capacity to endure forces that occur in the human hip over decades.

Results from the Nordic Arthroplasty Register (NARA) show that biological fixation with uncemented components is superior to cemented fixation, in patients 45-79 years of age, with a lower odds ratio for aseptic loosening (4). Biological fixation is achieved by initial press fit, i. e. fill of the implant into a preformed cavity in the host bone. The initial press fit secures primary stability of the implant mechanically. Secondary fixation will be achieved by bone osseointegration, a biological chemical or microinterlock bond, between bone and implant. Albrektsson and Brånemark showed that this phenomenon, referred to as bone ingrowth, occurred by direct structural and functional connection between bone and the surface of the implant (5). With the resolution of an electron microscope apposition of calcification to the titanium oxide at the surface of a titanium implant can be seen (6), (Fig. 2) The strength of the bond is of the same magnitude as bone itself.

For patients with good bone stock a shift towards

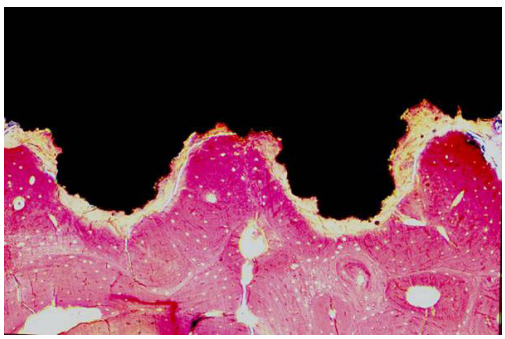


FIG 2. *Osseointegration.*

Introduction

biological fixation of the components in THA is ongoing. Even though long term fixation is superior with biological fixation, there are some issues with uncemented implants. During the first two years after surgery there is an increased risk of periprosthetic femoral fractures (4) and this is an important limitation in the use of uncemented implants. Bone stock has to be strong enough to withstand the forces from impacting these implants during surgery. During rehabilitation, before biological osseointegration has occurred, the bone stock also has to withstand the forces from loading the initially mechanically fixed implants. Osteoporosis or compromised bone stock for other reasons are relative contraindications for using uncemented implants in hip arthroplasty surgery. Once biological fixation has been achieved, no difference in the incidence of periprosthetic femoral fractures can be seen during the period 2-16 years after surgery (4).

Revision hip arthroplasty

Data from the Annual report of 2011 from Swedish Hip Arthroplasty Register (1) show that aseptic loosening of the components is the predominant reason for revision surgery with a proportion of 56%. Infection (12%), dislocation (12%) and periprosthetic fractures (8%) accounts for approximately one-third of the revisions, (Table 2).

However, the reasons for failure leading to revision hip surgery are changing. Aseptic loosening of the components is decreasing and both periprosthetic fractures and infections are increasing.

Surgical options in femoral hip revision surgery are cementing a new component, either with or without the addition of impacted morselized allograft bone, or biological fixation with uncemented components. Recementing a component might be chosen in elderly patients with low functional demands. In active patients with poor bone stock, hip revision with impacted morselized allograft bone has shown good long-term results (7, 8), but the technique is technically demanding and time consuming. In patients with severe bone loss, good bone restitution with impaction bone grafting has been reported. However, high complication rates, especially due to periprosthetic femoral fractures, have also been reported with this method (9). Hip revision surgery with re-cementation of implants, with or without bone grafting, fall outside the scoop of this thesis, as do acetabular revision surgery, even though complications with the acetabular component are the major problem in contemporary uncemented THA (10-12). Possible efforts to improve the outcome of the actebular component are discussed in study V but, in this thesis, hip revision surgery will focus on uncemented femoral revision with proximally coated stems (study I and II).

A loose femoral stem will compromise proximal femoral bone stock. Most uncemented stems used in revision surgery are therefore designed to bypass the proximally damaged zone and to achieve initial stability from press-fit distally. Clinical results with these types of stems have been excellent (13-16). The main drawback is the transfer of excessive load distally, leading to further deterioration of proximal bone stock. Severely compromised bone stock will influence the outcome after hip revision surgery with increased risk of periprosthetic fractures and perhaps implant loosening (17). Besides this, it also contributes to more technically demanding revision surgery with increased risk of surgery related complications.

From what is mentioned above it is prudent to be as conservative as possible, both in primary and revision hip arthroplasty and always be aware of a pos-

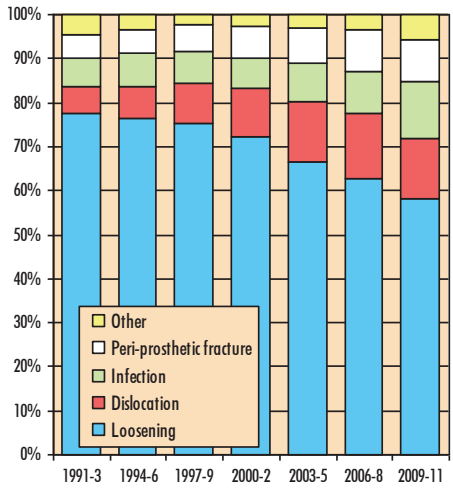


TABLE 2. *Reprinted with permission from the Swedish Hip Arthroplasty Register (SHAR).*

Introduction

sible need for further surgery. Using stems designed for proximal fixation, the goal of being conservative can be achieved. Outcome with proximally coated tapered stems in hip revision have shown promising results if bone loss at revision was mild to moderate (18-20).

In study I in this thesis, we evaluated the medium term outcome after aseptic femoral revision surgery with a proximally porous- and HA-coated uncemented tapered stem.

Periprosthetic bone remodelling

STRESS SHIELDING

Bone is a living tissue that remodels continuously, adapting itself to the local environment in the skeleton. This so called adaptive bone remodelling is a physiological process enabling the skeleton to withstand the load forces acting upon it. For biological reasons, bone that is not loaded, i. e. not needed, will diminish and bone that is over-loaded will increase, both in regard to volume and bone mineral density. These fundamentals of bone remodelling are referred to as Wolff´s law (21). Uncemented total hip arthroplasty (THA) implies periprosthetic bone resorption to a level higher than that of normal ageing but the extent and distribution of BMD changes differ between different stem types (2, 22). The mismatch in modulus of elasticity between the prosthetic components and the surrounding bone off-loads certain periprosthetic regions (23-26). In the femur load is transferred distally, off loading the proximal regions, and in the pelvis load is primarily transferred to the acetabular rim, off-loading the central acetabular regions. This adaptive bone remodelling-phenomenon is referred to as "stress shielding" and relates to bone being shielded from load by adjacent stiffer metal implants. Stress shielding is a key subject in this thesis. The eventual fragile periprosthetic bone may limit the longevity of the hip replacement due to periprosthetic fractures (27, 28) and avulsions of tendon and muscle insertion. Periprosthetic fractures are expected to be a more common mode of failure in THA in the future, as younger patients are undergoing surgery and, hence will live with their hip prosthesis for longer periods of time (Fig. 3 and 4).

Attempts to reduce stress shielding-mediated adaptive bone resorption can be achieved pharmacologically with bone metabolism-interacting agents such as bisphosphonates (commented in study III) (29-32), with prosthesis design (commented in study IV) (33-35) and with component surface coatings (commented in study V) (36-39).

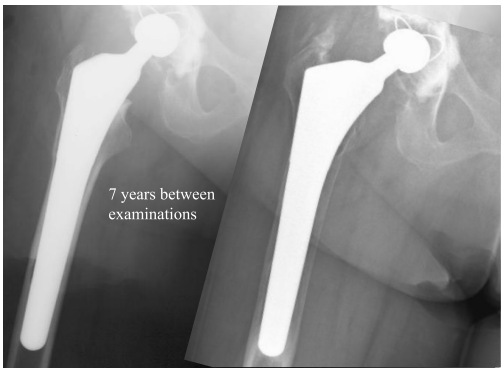


FIG 3. *Note the pronounced reduction in cortical bone around the stem as a result of adaptive bone remodelling).*

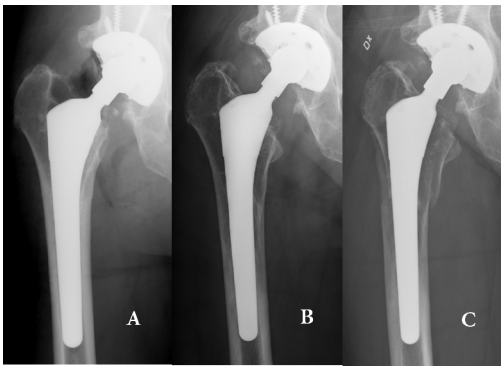


FIG 4. *Disuse atrophy due to stress-shielding. Postoperatively (A). At 4 years (B) there are obvious signs of stress-shielding with disuse bone atrophy proximally. After 5 years the patient sustained a periprosthetic fracture after minimal trauma (C). The fracture was fixed with open reduction and internal fixation. The stem was not revised..*

OSTEOLYSIS

In contrast to stress shielding, which is a physiological process, osteolysis is a pathological process leading to degradation of bone tissue (Fig. 5). The dominating mechanism for bone degradation is the inflammatory response to wear debris (40). The major source of wear debris in contemporary THA is polyethylene (PE) particles being torn away from the articulating

Introduction

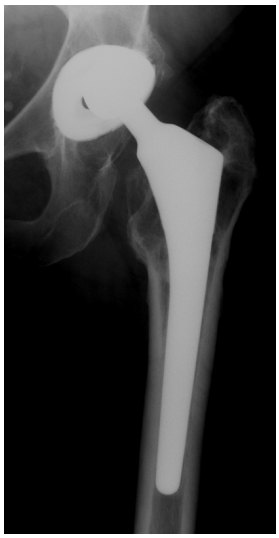


FIG 5. *Signs of focal osteolysis proximal to the cup and proximally around the stem. Note also the asymmetrical position of the head as a result of polyethylene wear.*

bearing surfaces (12). Several studies have pointed to the association between peri-implant bone loss and inferior long term outcome in THA (41, 42). The association between periprosthetic osteolysis in uncemented THA and implant failure does not appear to be as strong on the femoral side (43, 44) as on the acetabular side (11, 45). Osteolysis is thought to be reduced by reducing polyethylene wear and subsequently, better long term outcome in THA is expected if wear characteristics of polyethylene can be improved. From wear studies, a stipulated threshold of an annually polyethylene wear rate above 0.2 mm has been suggested to be likely to induce periprosthetic osteolysis (42, 46). Dumbleton et al carried out a literature review to investigate the association of PE wear rate and development of osteolysis (47). They drew the conclusion that a higher wear rate was associated with increased osteolysis and that a threshold of PE wear rate less than 0.05 mm annually, was less likely to induce osteolysis. In study V polyethylene wear rate in two different highly cross-linked polyethylene (HXLPE) liners is compared in a randomized controlled trial.

There has been speculation as to whether stress shielding-mediated bone loss contributes to, or works synergetically with, the development of osteolysis. It may be logical to think that atrophic, stress deprived bone, with low bone mineral content, would be particularly sensitive for bone degradation secondary to wear debris-mediated osteolysis. However, as yet, there is no clear scientific evidence of such a pathogenesis.

BISPHOSPHONATES ON BONE REMODELLING

It is obvious from what is mentioned above that periprosthetic bone loss is a risk factor for deteriorating long term outcome in THA. Bisphosphonates have a strong antiresorptive effect on bone tissue via an osteoclast-apoptosis-mediated effect. There is a strong affinity for bisphosphonate to hydroxyapatite in bone mineral and when osteoclasts phagocytos bisphosphonate-containing bone they lose their bone resorptive capability.

The result of diminished bone resorption and on-going bone production by osteoblasts, means the net effect will be an increase in bone mineral density (BMD).

Bisphosphonates are used clinically for treatment of osteoporosis, Paget´s disease and in malignancies with increased bone turnover. In the orthopaedic field, it is used to reduce the risk of osteoporosis fractures in the vertebrae, hip, proximal humerus and distal radius (48-51). Over the last decade, several studies have focused on the effect of bisphosphonates on bone remodelling adjacent to orthopaedic implants. These studies reveal a positive bone-sparing effect of bisphosphonates (30, 31, 52) but the effect appears to be temporary. After cessation of the drug, BMD tends to decrease and extensive long term reduction in BMD loss have not been consistently recorded (30). However, the pattern of long term changes in bone mineral after use of bisphosphonate treatment is mixed (53). Apart from influencing periprosthetic bone remodelling, treatment with bisphosphonate has also been shown to enhance implant fixation. Migration of the tibial component in cemented total knee arthroplasty could be reduced after oral (54) and local bisphosphonate treatment. Reduced migration in uncemented acetabular components in THA was recorded after postoperative injection of zoledronic acid (55). The ability of bisphosphonates to reduce initial implant migration, and enhance early component fixation, could be a highly beneficial parameter for improved outcome in joint replacement surgery, when circumstances for implant survival are suboptimal. Up to now, no algorithm when to use bisphosphonate treatment in joint replacement surgery is present.

Introduction

Biomaterials in total hip arthroplasty

Hip replacement surgery requires implantation of artificial materials into the human body. A biomaterial is a non-viable material used in a medical device intended to interact with biological systems (56). Biomaterials relevant to this thesis are metals, ceramics and polymers.

METALS

The ideal femoral implant in hip arthroplasty would be an implant with the same modulus of elasticity, i. e. same stiffness, as bone itself and with a permanent strong attachment to bone, to endure the local forces acting on the skeleton. In such a scenario, load transfer during walking would be evenly distributed in a physiological pattern from the artificial articulating head through the implant to the surrounding periprosthetic bone (Fig. 6). At the same time the implant must be tough enough to withstand the compressive and bending forces acting on it during ambulation. Research in the area of modern hip replacement can assist in the development of such a device. As the ideal solution is still lacking, other alternatives have been used with varying success.

STAINLESS STEEL

Stainless steel, an iron-based alloy containing about 20% Chromium, 17% nickel, and Molybdenum, is tough enough to endure the forces acting on a hip artroplasty but the modulus of elasticity is ten times higher than that of bone. For reasons related to stress shielding this makes it unfavorable to use for biological fixation but it is commonly used in cemented THA.

COBALT-CHROME

Cobalt-Chrome-alloys (CoCr) are widely used in orthopaedic implants today. These alloys usually contain 30-60% cobalt, 20-30% chromium, 7-10% molybdenum, and various amounts of nickel. By roughening the CoCr-surface with either porous coating (39) or sintered fiber metal (38) bone ingrowth into the metal surface can be achieved, enabling use of CoCr-implants for cementless endoprosthesis purposes. However, this alloy is also much stiffer than bone and will induce pronounced adaptive bone remodelling of the periprosthetic bone. Because of the high corrosion and fatigue resistance of a CoCr-alloy, it is ideally suited for articulating surfaces such as the artificial articulating head in hip prosthesis (57). It is also commonly used in cemented femoral stems, an area which lies outside the scope of this thesis.

TITANIUM AND TI-6AL-4V

Pure Titanium (Ti) is a very biocompatible metal (5). The modulus of elasticity is closer to that of bone but still about five times higher than cortical bone. Compared to CoCr-alloys, not only the elastic modulus but also strength is reduced. By adding 6% aluminium and 4% vanadium an alloy (Ti-6Al-4V) with excellent mechanical and biocompatible properties are manufactured. Ti-alloy is the most predominately used substrate for biological fixation of endoprosthesis components in the world today (58). Fixation is enhanced by increasing the porosity of the Ti surface, and thereby the roughness and the area for ingrowth, with beaded microspheres,

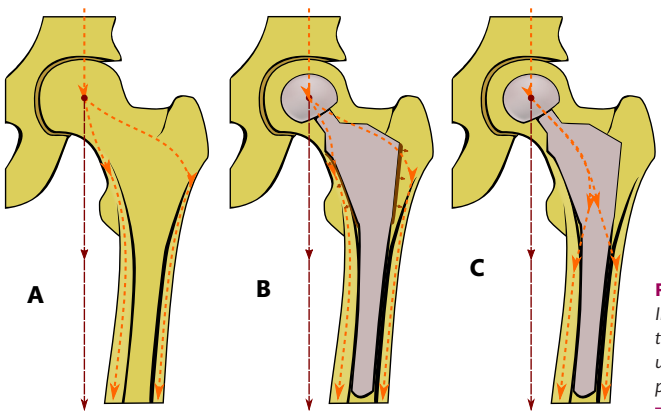


FIG 6. *The coveted proximal fixation*
In A the load on the normal femur. B after insertion of a stem with proximal fixation and C the usual result; distal fixation and off-loading of the proximal femur.

Introduction

sintered metal fibers or plasmasprayed titanium substrates (59). It has also been shown that blastered Ti, with a roughness of only 5-7 µm, also provides a reliable substrate for bone ingrowth (60, 61).
Development of new substrates of metal surfaces have come to clinical use lately. This is thought to be of specific importance in situations where patients´ bone stock is severely compromised. Several manufacturers of orthopaedic implants have developed a metal coating aimed at enhancing bone ingrowth. The average porosity in the materials is as high as 60-80% and the continuous three-dimensional scaffold matrix with enhanced interconnecting porosity resembles the microarchitecture of trabecular cancellous bone (62). The substrates available today are made of Titanium or Tantalum (63). The porous titanium construct will be discussed in paper V in this thesis.

CERAMICS

Under physiological conditions the surface of a titanium implant is oxidized and covered with several layers of titanium oxide. The oxidized surface resembles a ceramic coating because of its stable, hard and very corrosion-resistant properties. This is probably an explanation for the excellent biocompatibility seen with Ti implants.

Bone consists of collagen and bone mineral. The latter counts for approximately two-thirds of the dry weight and consist predominately of different compositions of calcium phosphates. The most prevalent form is hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$ (Fig. 7). By coating the surface of metal implants with calcium phosphate ceramics, a bioactive layer is introduced in the interface between metal and bone. The aim of this bioactive layer is to facilitate and enhance bone formation to ensure extensive and reliable osseous fixation of an implant. The HA coating will gradually be dissolved and replaced by new bone in the delicate balance of bone remodelling. HA has been shown to be osteoconductive and to increase the mechanical strength between the implant and the bone (64). Bone ingrowth is also facilitated by the presence of HA when micromotion is present and when there is a gap between the implant and the bone (65-67). This commonly occurs initially after press fit implantation. If primary stability of the implant is not fully achieved by the press fit fixation micromotion of the implant may occur. This could lead to failure of implant fixation or to fibrous fixation instead of osseous integration (65, 68). HA has the capability, to a higher extent than in a non-HA-present situation, to convert initial fibrous tissue in the interface to bone (69).

Apart from facilitating bone ingrowth of metallic implants, HA could also contribute to a reduction in periprosthetic osteolysis. The tight bond between the HA-coating and the surrounding bone has been shown to seal the interface between the implant and the host bone (70, 71). Thus, preventing wear debris from the joint articulation from migrating into the interface and causing local bone loss (osteolysis).

Despite the positive effects of HA-coating on bone formation and implant fixation (36, 72-74), results from clinical studies focusing on long term prosthesis survival cannot confirm better outcome with HA-coated implants compared to other well functioning non-HA-coated components (61, 75-78). On the contrary, there are some concerns about mechanically detached HA-particles causing abrasive third-body wear of joint articulation surfaces (79, 80) and delamination of HA-coatings which could jeopardize implant fixation (81, 82). This is discussed more extensively in the section "Discussion on materials".

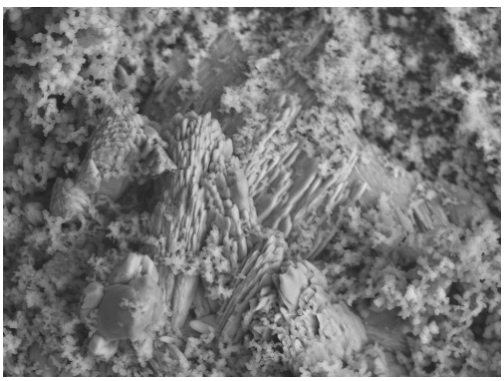


FIG 7. *Hydroxyapatite particles seen in scanning electron microscope.*

Introduction

POLYMERS

The gold standard of bearing surfaces in joint articulation in THA, at least in the Nordic countries, is still a metal head articulating in an all polyethylene cup or in a polyethylene liner in an uncemented shell. Polyethylene (PE) is an excellent material for this purpose because of its physical and chemical properties. It has a low friction coefficient, high impact absorption capacity and is inert to local chemical reactions.

Older types of PE have shown signs of considerable wear after years in vivo (83). As mentioned above, in the light of younger and more active patients living with a hip prosthesis for longer periods of time, there is a need for improved wear characteristics of the polyethylene, to improve the long term outcome of THA. At the end of the 1990s, a new type of PE material was developed. By increasing the dose of gamma irradiation, cross-linking between the polymer-chains could be increased and, as a result of this, the wear characteristics were dramatically improved in laboratory tests (84, 85). Also, in clinical settings the new type of highly cross-linked polyethylene (HXLPE) has shown reduced wear (86-88). The drawback with an increased dose of irradiation is that the amount a free radicals, emerging from the cascade reaction triggered by the cross-linking irradiation, also increases. It is important to neutralize these to prevent oxidation of the polyethylene. Oxidation will degrade the PE with reduced toughness and reduced crack fatigue resistance as a consequence (89). By reheating the PE after the cross-linking procedure free radicals can be neutralized. There are two ways of doing this, either by annealing or remelting the PE. The pros and cons with each method are more thoroughly discussed in "Discussion on materials".

A second generation of highly cross-linked polyethylene has been developed during the last 5-7 years. The anti-oxidant, α-tocopherol (vitamin E) is used to neutralize the free radicals emerging from the cross-linking irradiation (90). This new vitamin E-diffused PE is now being tested worldwide. Our results from a randomized controlled trial of the characteristics of this material are presented in study V.

Polyethylene is a viscous-elastic material with the capability to deform under stress. The deformation is slow and made possible by long polymer-chains sliding up on each other. This phenomenon of slow deformation under stress is referred to as creep and has nothing to do with polyethylene particles being torn away from the PE surface. How long this process continues after THA surgery is not completely clear, but it is thought to play a role during the first six to twelve months after surgery (91-93). Probably, different types of PE differ in their creep properties as well. After the creep process is over, PE wear rate is approximately linear, in a steady-state mode, for several years (91). A correlation between PE wear and periprosthetic bone loss due to osteolysis has been advocated for a long time and there are several studies concluding this (41, 42, 46, 47). The mechanism of bone loss secondary to PE wear is mediated through the inflammatory response on abraded PE-particles, leading to periprosthetic bone degradation. Reducing polyethylene wear by the use of more wear resistant HXLPE is thought to be a crucial factor in diminishing periprosthetic osteolysis and thereby improving the long term outcome in THA.

4 AIMS

The general aims of the studies were to investigate bone remodelling around, and fixation of, uncemented implants in primary and secondary hip replacement surgery. We also wanted to assess the clinical function after total hip arthroplasty.

THE SPECIFIC AIMS WITH EACH STUDY WERE:

Study I: To study the clinical and radiographical outcome after femoral hip revision surgery for aseptic loosening using a tapered uncemented proximally porous- and hydroxyapatite-coated stem.

Study II: To study the periprosthetic adaptive bone remodelling around a tapered uncemented proximally porous- and hydroxyapatite-coated stem after femoral revision surgery.

Study III: To study the effect of oral risedronate on femoral periprosthetic bone resorption after total hip arthroplasty in patients with hip osteoarthritis when using a tapered uncemented proximally porous- and hydroxyapatite-coated femoral stem.

Study IV: To compare an ultra-short wedge shaped uncemented stem to a tapered proximally coated conventional uncemented stem with respect to periprosthetic adaptive bone remodelling and implant migration patterns.

Study V: To compare an acetabular component with a three-dimensional titanium porous construct backside and E-vitamin-treated highly cross-linked polyethylene liner to a conventional titanium acetabular component with porous- and hydroxyapatite-coated backside and highly cross-linked polyethylene liner with respect to periprosthetic adaptive bone remodelling, implant migration patterns and polyethylene wear.

5 HYPOTHESES

Study I: Femoral hip revision surgery with a proximally coated uncemented tapered stem is a reliable procedure with good predictable mid-term results if bone defects at revision are moderate.

Study II: Adaptive periprosthetic bone remodelling is pronounced after femoral hip revision with a proximally coated uncemented tapered stem.

Study III: Oral risedronate once weekly for 6 months after THA will reduce the periprosthetic bone resorption around an uncemented tapered stem, up to 2 years after surgery.

Study IV: An ultra-short wedge shaped uncemented stem reduces periprosthetic bone loss compared to a conventional uncemented stem, up to 2 years after THA.

Study V: An acetabular component with a three-dimensional porous titanium construct backside reduces periprosthetic bone loss compared to a titanium acetabular component with conventional porous- and hydroxyapatite coated backside, up to 2 years after THA.

Patients

6 PATIENTS

Patients

STUDY I - II

Between 1989 and August 2011, 2223 THA were performed using an uncemented femoral stem at Danderyd Hospital. Patients included in this thesis were all recruited from this population (Fig. 8, Table 3).

During the time period 1989 to 2002, we used different surgical techniques to perform femoral revisions after aseptic implant loosening. In rare cases, after a risk-benefit analysis, we re-cemented a new stem in place when treating elderly patients with low functional capacity. The most frequently used surgical procedures were cemented impaction bone grafting (IBG) and press fit fixation of uncemented stems. The former was used in all cases when bone defects at revision were pronounced. The latter was used only when bone defects at revision were mild to moderate. All patients in the latter group, who underwent surgery with a proximally coated unce-

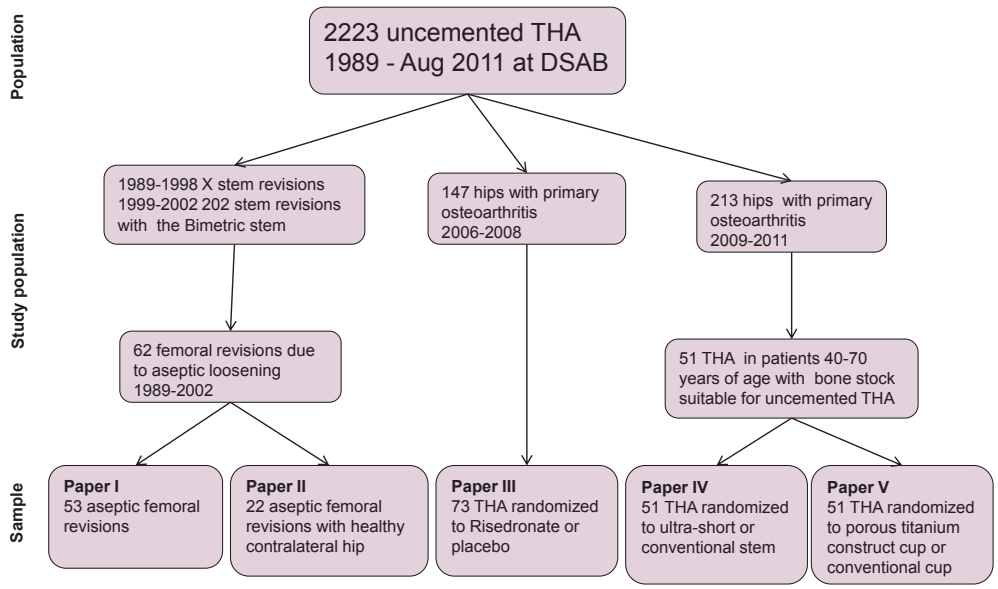


FIG 8. ***Flow chart of all patients included in this thesis***

TABLE 3. ***Patients characteristics in study I-V compared to patients characteristics in Swedish Hip Arthroplasty Register, Annual Report 2011***

	SHAR 2011†	Study I	Study II	Study III		Study IV & Study V	
		n=60	n=22	(n=36) risedronate	(n=37) placebo	(n=26) proxima/ pinnacle	(n=26) bimetric/ regenerex
Gender, ♂/♀	(%) 42 / 58	37 / 23	13 / 9	14 / 22	16 / 21	11 / 15	11 / 14
Age*	♂ 67 / ♀ 69	65 (35-84)	75 (63-83)	61(41-69)	61(41-69)	62 (50-70)	62 (51-70)
Body Mass Index	27	27 (18-39)	27(18-36)	27 (22-36)	28 (20-45)	27 (20-35)	28 (22-34)
Charnley category, 1/2/3	(%) 58 / 42	17 / 11 / 25	13 / 0 / 9	20 / 13 / 3	16 / 16 / 5	16 / 10 / 0	18 / 7 / 0
ASA, 1-2/3-4	(%) 85 / 15	29 / 22	16 / 6	35 / 1	34 / 3	21 / 5	20 / 5

* Mean (range). Age at follow-up in study I-II, age at surgery in study III-V
†SHAR = Swedish Hip Arthroplasty Register Annual report 2011

Patients

mented tapered stem, constituted the study cohort of 60 patients (62 hips) included in **study I**. We were able to evaluate 53 hips in 51 patients. Patients in **study II** were recruited from the same cohort. Only those 22 patients in study I that had surgery primarily (index operation) for primary ostheoarthritis, and had a healthy hip on the other side, were included. The mean time from surgery to follow-up in these two retrospective longitudinal studies was 6 years.

STUDY III-V

Patients included in the prospective randomized controlled trials in **studies III-V,** were 40-70 years of age with primary OA and bone stock suitable for cementless THA, i. e. femur type Dorr A or B (94). Exclusion criteria were previous hip surgery on the affected side, medical conditions or medications that could influence BMD, i. e. glucocorticosteriods, bisphosphonates or cytostatic drugs taken on a regular basis six months prior to surgery. Between 2006 and 2008, patients planned for uncemented THA because of primary OA at Danderyd Hospital were recruited to study III. After inclusion for study III was completed, patients were recruited to study IV and V during the years 2009 to 2011, (Fig. 9).

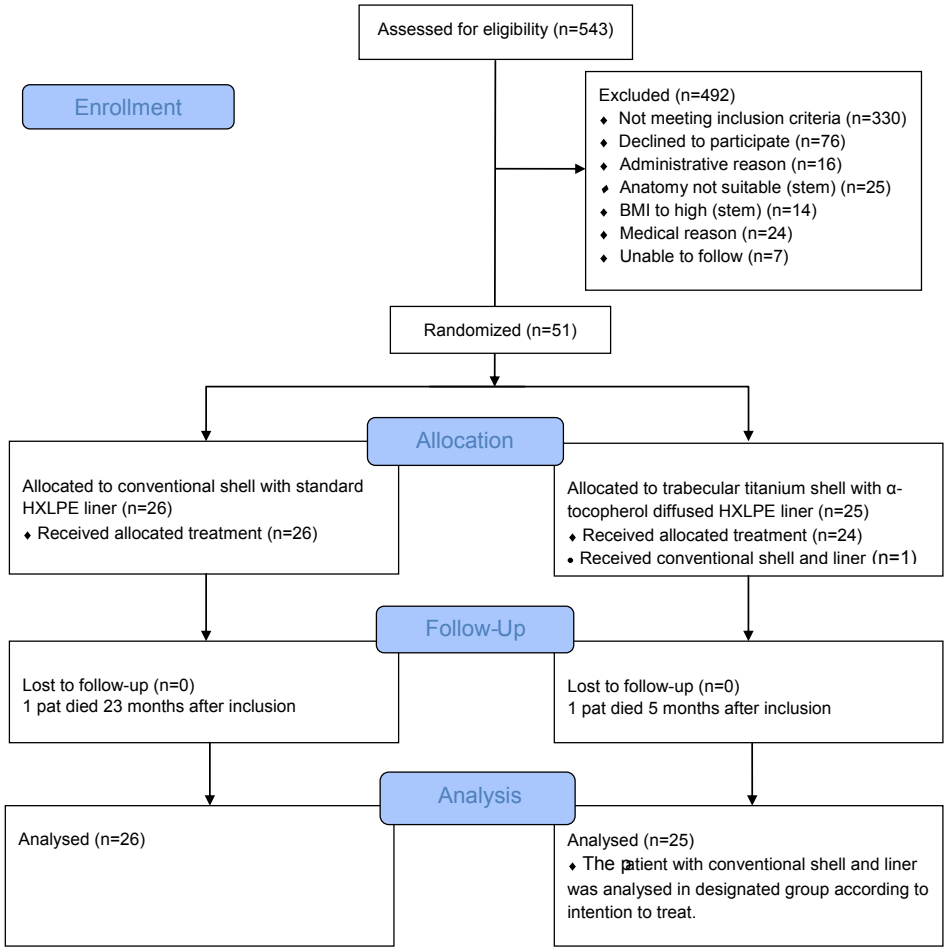


FIG 9. ***Consort flow chart of patients in study V***

7 MATERIALS

Only uncemented implants were evaluated in the studies in this thesis. Two types of hydroxyapatite coated titanium femoral stems, (Table 4) and two types of titanium acetabular cups with differing properties regarding shell backside surface coatings and polyethylene articulating liners have been evaluated, (Table 5).

TABLE 4. ***Stem characteristica.***

Stem Properties	Proxima®	Bimetric®
Design Material Coating	Anatomically wedge shaped Titanium alloy (Ti-6Al-4V) Fully porous coated with sintered beads, mean pore size 250 µm, covered with hydroxy-apatite (thickness 30 µm, highly amorphous, Duofix™) Distal tip textured.	Straight tapered (3°), collarless Titanium alloy (Ti-6Al-4V) Proximal 25% porous coated, mean pore size 300 µm, covered with plasma-sprayed hydroxy-apatite (thickness 40–70 µm, crystallinity 50–70%, purity >95%) Distal 75% grit-blasted with 6.9 µm roughness.
Stem lengths used,	71-83 mm	130-155 mm

TABLE 5. ***Characteristica of the acetabular implants evaluated in study V.***

Cup Properties	Regenerex® + E1-poly® liner	Pinnacle® + Marathon® liner
Design	Hemispheric press fit shell, RingLoc® liner locking mechanism	Hemispheric press fit shell, Tapered liner locking mechanism
Material	Titanium alloy (Ti-6Al-4V)	Titanium alloy (Ti-6Al-4V)
Coating	Regenerex®, porous titanium 3D-construct, thickness 1,5 mm, average porosity 67%, mean pore size 300 µm	Duofix®, three layers of pure titanium sintered beads, mean pore size 250 µm, plasma-sprayed highly amorphous 35 µm thick HA
Articulation	Polyethylene HXLPE liner, 10 Mrad gamma irradiation, α-tocopherol diffused, CoCr modular head, 32 mm diameter	Polyethylene HXLPE liner, 5 Mrad gamma irradiation, CoCr modular head, 32 mm diameter
Manufacturer	Biomet Inc., USA	DePuy Orthopaedics, Inc., Johnson&Johnson, USA

BIMETRIC STEM

The Bimetric® stem (Fig. 10) was used in studies I-V. It has a circumferential proximal plasma-sprayed porous and HA-coating. It is tapered in three dimensions, in the frontal plane, sagittal plane but also from the lateral shoulder to medial calcar.

The stem is available in proportional sizes from 7 to 19 mm with corresponding lengths from 115 to 175 mm. In study I and II there was only one standard offset stem available. A modular cobalt-chrome head of varying neck extension lengths have been used. Head diameters in study I-II are 22 or 28 mm, in study III 28 mm and in study IV-V 32 mm.

FIG 10. *The proximally porous- and hydroxyapatite coated tapered Bimetric stem. Note the towers with Tantalum beads for RSA analysis. Photo by Carin Wesström.*

PROXIMA STEM

The Proxima® stem (Fig. 11), was used in study IV and V. The stem is a result of the combined properties from an earlier stem, IPS®, and a successive shortening of an initially custom made stem developed by Prof. Santori, Rome, Italy, (95). The aim was to develop a stem that could reduce stem-mediated stress shielding. Because of its very short length it was thought to shield less femoral bone. This is discussed extensively in paper IV. The stem is available in 8 proportional sizes with increasing lengths and offsets, ranging from 67 to 86 mm in length and from 38 to 52 mm in offset. Design rationales for the ultra-short stem are an anatomically wedge shape, a prominent lateral flare and absence of a diaphyseal stem. These features are claimed by the manufacturer to provide initial stability both vertically and rotationally and together with a high horizontal neck resection ensure load transfer to both the medial and lateral aspects of the proximal femoral metaphysis (96-98). The macrotexture of the surface is stepped to increase the area for ingrowth and to transform tangential forces into compressive loads to the bone (99).

FIG 11. *The porous- and hydroxyapatite coated anatomic ultra-short Proxima stem. Photo by Carin Wesström.*

REGENEREX CUP AND E1-POLY LINER

The Regenerex® cup, (Fig. 12), is a press fit hemispherical acetabular implant made of titanium alloy. It has a solid titanium shell coated with a three dimensional (3D) porous titanium construct backside surface. The specific characteristics of the new coating architecture are described in Table 5. Design rationales for the 3D porous titanium construct backside are to increase friction, porosity and compressive strengths and at the same time maintain a modulus close to cancellous bone. These features are claimed by the manufacturer to increase initial stability and to enhance bone ingrowth into the titanium construct. With increasing diameter in cup size, titanium shell thickness is also increased but the thickness of the coating stays constant at 1.5 mm for all diameters of the shell.

FIG 12. *An acetabular shell with a porous titanium construct coating (Regenerex) and an α-tocopherol treated highly cross-linked polyethylene liner (E1-poly)*

The acetabular implant used in study IV and V had holes for additional screw fixation. In only one case did we use a screw to enhance fixation. The screw holes not used were left open.

Together with the Regenerex shell we used a HX-LPE liner that had been treated with an anti-oxidant, α-tocopherol. The rationales for α-tocopherol treatment of the PE is to conserve the improvements in wear characteristics that crosslinking of the PE with gamma irradiation give (100). At the same time, the irradiated PE gains oxidative stability because of the eradication of free radicals. This is more thoroughly explained in the section Discussion on polymers.

PINNACLE CUP AND MARATHON LINER

The Pinnacle cup and Marathon liner, (Fig. 13), were used in the control group in study V. It is a clinically well proven acetabular implant (101) with documented low PE wear rate (85, 92). Characteristics of the shell and liner are presented in (Table 5). The HA layer is highly amorphous, low crystalline and only 35 µm thick. The purpose for this, according to the manufacturer, is that the HA should not occlude the pores of the underlying porous coating of sintered Titanium beads, and thus should not impair bone in-growth.

The shell we have used had holes for additional screw fixation which we did not use. The screw holes were left open. ⊙

FIG 13. *The Pinnacle cup with porous- and hydroxyapatite coating and a highly cross-linked polyethylene liner (Marathon). Photo by Carin Wesström.*

8 METHODS

Surgery

SURGICAL TECHNIQUE AND PERIOPERATIVE CARE

In studies I-V we used a standard posterolateral approach as described by Moore (102). Except for the operations performed during the first years in study I and II we also repaired the posterior capsule and external rotator muscles (103). Preoperative templating was performed by drawing on radiographic films in study I and II, and with a software for templating in studies III-V (mDesk®, RSA Biomedical, Umeå, Sweden).

In studies IV-V we inserted Tantalum beads, 1 mm in diameter, well spread out in the periacetabular region as well as in the proximal femur. We aimed to insert 9 beads in each segment using a spring-loaded insertion device with inside-out and outside-in technique. We also inserted beads peroperatively in the outer rim of the PE liner in an attempt to enhance precision for the edge detecting markerless RSA measurements.

Prophylactic antibiotics (CloxacillinR, Meda, Sweden) were given to all patients 30 minutes prior to the start of surgery and it was repeated 3 times during the first 24 hours postoperatively. To all patients in studies III-V intravenous tranexamic acid (CyclokapronR, Pfizer, Sweden) was administered before the start of surgery to reduce bleeding. In study IV-V local infiltration analgesia with ropivacain, ketorolak and epinephrine was given peroperatively in the soft tissues to minimize postoperative pain. To reduce the risk of thromboses Dextran was given preoperatively in all patients and postoperatively every second day until mobilization was achieved in studies I-II. Patients in studies III-V was given daltaparin (Fragmin®, AstraZeneca, Sweden) for 7 up to 28 days after surgery depending on individual risk assessment of postoperative thrombosis.

REHABILITATION

The rehabilitation protocol for patients in studies I-II was individualized depending on the degree of preoperative bone loss and initial fixation of the implants. In study III-V full weight-bearing was allowed as tolerated and crutches were recommended during the first weeks after surgery according to each patient's preference. Rehabilitation was supervised by a physiotherapist on the ward and thereafter in an outpatient clinic during the first weeks.

Radiographic evaluation

Radiographic assessment of hip replacements plays a major role in studies I-III in this thesis. According to the standardized technique of radiographic evaluation recommended by the Swedish Orthopaedic Association (104) three exposures were taken at every follow-up. That is an antereoposterior (A-P) and a lateral view of the hip and an A-P view of the pelvis. We compared consecutive radiographs taken immediately before and after surgery, and all radiographs taken thereafter during follow-up.

STUDY I-II

In studies I-II we analyzed the radiographs in order to address three particular issues. Firstly, we classified bone defects prior to revision surgery, secondly, we assessed stem fixation, and thirdly, signs of periprosthetic bone remodelling.

Bone defects were classified according to the classifications of Gustilo and Pasternak (105) and Endo-Klinik (106) (Fig. 14). These classification systems are described in more detail in Discussion on methods.

Assessment of fixation and bone remodelling was done according to the criteria of Engh et al (107). This instrument differentiates the assessed radiographic parameters into either two signs predicting osseous fixation or six signs predicting implant stability, i e a well fixed implant with expected fibrous fixation. Signs of osseous fixation are endosteal bone bridges (spot welds), predominately in the coated region of the implant, and absence of reactive lines

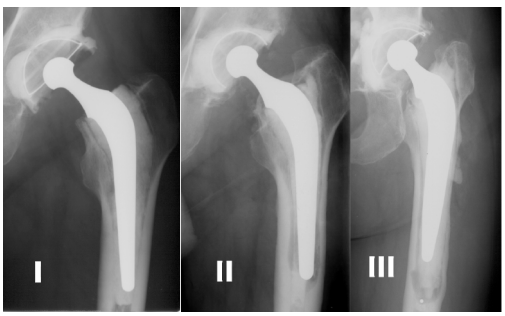


FIG 14. *Aseptic loosening with bone defects type I, II and III according to Gustilo-Pasternak and Endo-Klinik classification systems*

along more than 50 % of the coated region. Signs determining stability are the appearance or absence of the following six parameters; reactive lines along the stem-bone interface in the non-coated region, pedestal formation at the tip of the stem, calcar atrophy, interface detoriation, implant migration and particle shedding from the stem surface (Fig. 15). Migration of the femoral implants was defined as a change in the vertical distance between the easily identified inferior border of the stem coating to the most medial point of the lesser trochanter or as any change in alignment or rotation. The subsidence was considered definite if the change was more than 4 mm (108). Bone remodelling assessed from consecutive radiographs in studies I-II were divided into "Stress shielding"-parameters, such as calcar atrophy and distal cortical hypertrophy and the appearance and dynamics of periprosthetic linear or focal osteolysis. Distal cortical hypertrophy was defined as enlargement of the external femoral diameter around the distal part of the prosthesis, compared to the postoperative x-ray.

Heterotopic ossification was graded from the A-P hip x-rays according to Brooker´s classification (109). This is a four level scale graded from the amount of ectopic calcification between the proximal femur and the pelvis. Grade 1 represents "islands" of calcifications in the soft tissues. In grade 2 the distance between femoral calcifications and the pelvic bone is >1 cm. In grade III the distance is <1 cm. Ankylosis is graded as 4.

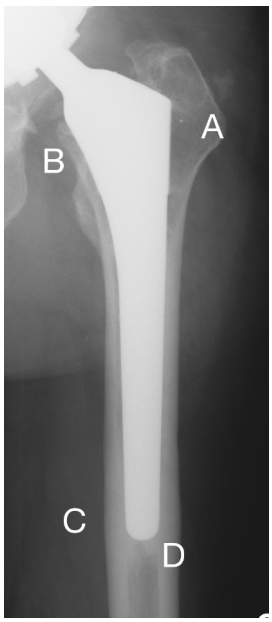


FIG 15. *Skeletal signs of bone remodelling, A: spot-weld, B: calcar atrophy, C: distal cortical hypertrophy, D: pedestal formation*

STUDIES III-V

In **study III**, implant fixation and bone remodelling was evaluated according to the above mentioned criteria of Engh et al (107) and stem migration was measured with Einzel-Bild-Röntgen-Analyse (EBRA) (110).

In **studies III-V** an important inclusion criteria was bone stock suitable for uncemented THA. We assessed bone quality according to Dorr classification (94). This classification is divided into three categories, and based on the appearance of shape and thickness of cortical bone in the proximal femur,. Category A has thick cortices on A-P and lateral x-rays and a taper-shape of the endosteal borders in the proximal medullary canal. Type B has thinner cortices than A, especially the posterior cortex on the lateral view, but a typical taper-shape of the endosteal borders at the level just below the lesser trochanter on A-P view. Type C has thin cortices on A-P and lateral x-rays and a stovepipe shape of the medullary canal. Femurs in category A and B were considered suitable for uncemented THA.

In **study V,** we measured pre- and postoperative offset in both groups from digitized radiographs using software (mDesk) from RSA Biomedical, Umeå, Sweden. We measured offset as the horizontal distance from the center of the head to the vertical midline of the proximal femur visualized on the AP hip radiograph.

EBRA

In study III, implant migration was measured with Einzel-Bild-Röntgen-Analyse (EBRA) (110). This is a method to evaluate THA component migration from consecutive plain radiographs. The software assesses consecutive digitized radiographs to calculate the migration in a 2-dimensional pattern (horizontal and vertical migration). Measurement of component migration is done from several reference points marked on every separate film (Fig. 16) The software has two features to improve accuracy of the measurements. Firstly, it compares whether

Methods

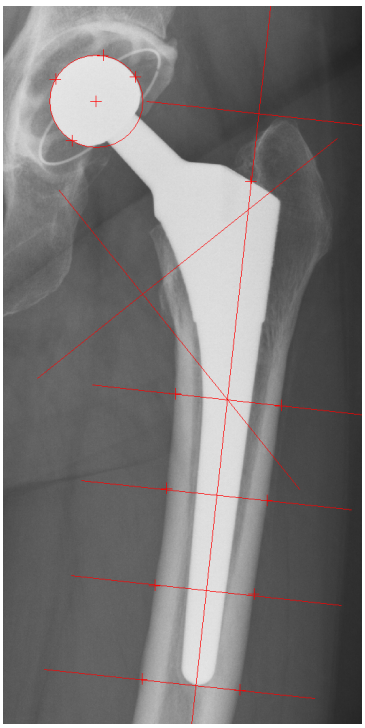


FIG 16. *Reference points and lines used in migration analysis with Einzel-Bild-Röntgen-Analyse (EBRA)*

consecutive examinations are comparable to each other from reference points of view. A default value between 1 and 4 mm, to be accepted as the largest distance between comparable reference points on consecutive x-rays, can be set. Secondly, the EBRA software gives examinations different weight in the analysis depending on the level of comparability. Migration calculated from examinations with high comparability gets higher weight in the component migration analysis.

Accuracy with the EBRA-method is for stem migration ±1.5 mm and for cup migration ±1.0 mm (110, 111). This is precise enough to do clinically relevant analyses of component migration in THA in order to detect patients that might have inferior outcome due to later clinical manifest loosening of components (112). In a study comparing EBRA to RSA the sensitivity of the EBRA-method was 100% to detect a migration of 1 mm and the specificity was 78% (111). The somewhat lower specificity was due to a tendency of EBRA to under-estimate migration compared to RSA-measurements.

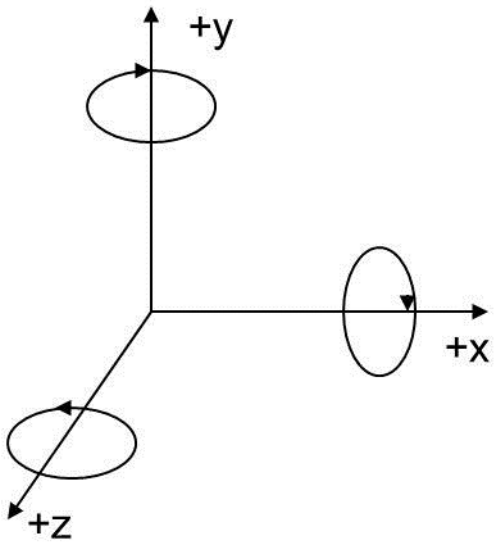
Radiostereometric analysis (RSA)

Radiostereometric analysis (RSA) (synonyms; Radiostereometry, Roentgen stereophotogrametric analysis) is based on the geometrical reconstruction of x-ray beams from calibrated stereo-radiographs (113). RSA is the gold standard for accurate measurements of component migration in six degrees of freedom, i e translation along and rotation around the x-, y- and z-axes. Component migration in THA is a valuable predictor for the outcome of long term fixation. An initial large or continuously on-going migration of an implant can predict later aseptic loosening (114-117).

The precision of RSA is, in laboratory conditions, close to perfect (118). In a clinical setting the precision is approximately 0.2 mm for translation along and 0.5° for rotation around the three axes in space. The high precision enables RSA to, from relatively few patients, determine whether an implant has a migration pattern that is coherent with migration patterns known to be well functioning.

The method requires peroperative insertion of radiodense markers in the skeleton as well as marking of the implants. For stems this should be done by the manufacturers but for acetabular components there are edge-detecting ellipse algorithms which can outline the outer diameter and the opening diameter of the metal shell. With these markerless techniques the position of a hemispherical shell can be calculated on calibrated radiographs (119).

The unique pattern of marker distribution in the pelvis, the proximal femur and the implant, outlines a rigid-body-shape called segment. Migration is determined by comparing the relationship of each segment´s centre of gravity between consecutive examinations. The irregular form of each rigid-body segment is expressed with the entity Condition Number (CN) (120). This entity is inversely correlated to the extent of distribution of the markers included in the segment, so the more spread out the markers are the lower the condition number will be. Preferably, to get accurate measurements of rotations around all three axes and translation along the z-axis, CN should be less than 100 when THA are evaluated (121). At least three consistent and stable markers in each segment are needed to perform accurate migration measurements. The entity expressing the stability of the shape of the segment is called



	Rotation	
	(+)	(-)
x-axis	anterior tilt	posterior tilt
y-axis	retroversion	anteversion
z-axis	valgus	varus

	Translation	
	(+)	(-)
x-axis	medial	lateral
y-axis	proximal	distal
z-axis	anterior	posterior

TABLE 6. *Labeling of the coordinate system defining micromotions of hip implants. With permission from Stergios Lazarinis.*

the "mean error of rigid body fitting" (ME). It measures the summarized discrepancies of each point in the rigid body between consecutive examinations. According to the standardized algorithm for RSA-measurements in hip arthroplasty ME should be less than 0.30 mm (121).

The coordinate system in which the measured migration is labeled is shown in (Table 6).

RSA IN THIS THESIS

Radiostereometry (RSA) was used in this thesis to measure implant migration in studies IV and V and to measure polyethylene wear in study V. We used one stationary and one mobile x-ray source (120 kV, 4-6 mAs) and a uniplanar calibration cage (Uniplanar digital 43, RSA Biomedical AB, Umeå, Sweden) to take digital calibrated radiographs (Bucky Diagnostics®, Philips, Eindhoven, Netherlands) (Fig.17) and we followed the published guidelines for reporting RSA results (121).

Before commencement of study IV, each of the ultra-short stems and the conventional stems were labeled with three Tantalum beads by the manufacturers. During surgery we marked the proximal femur with up to nine 1.0 mm Tantalum beads as well. Our plan was to compare stem migration in six degrees of freedom for the two stem types. Because of uneven distribution of stem sizes in both groups, i.e. some sizes were used more than others, we ran out of Tantalum beads-labeled stems. As a consequence of this, stems available for segment motion analysis were unevenly distributed, making group analysis of migration in six degrees of freedom unreliable. However, we could evaluate differences in overall magnitude of migration by calculating maximum total point motion (mtpm). This was done by calculating the 3-D translation vector of the femoral stem marker that had the largest movement, i. e. centre of the prosthesis head, in relation to the segment formed by the markers in the proximal femur. Complementary to the 3D mtpm-measurements we measured varus migration by calculating the hypotenuse with Pythagoras theorem from point migration along the x- and y-axes. The mean condition number was 38 (median 38, range 17-120) and the mean numbers of markers used in the femoral reference segment was 6 (median 6, range 4-9). Mean error of rigid body fitting was <0.3 mm.

In study V the periacetabular bone was marked with up to nine, well distributed, 1 mm in diameter, Tantalum spheres to form a rigid body segment. The cup segment was measured with the edge-detecting

Methods

marker-less technique mentioned above (119). Peroperatively, we inserted Tantalum marker beads in the peripheral rim of the polyethylene liners as well. One to 3 consistently visible liner beads were used in conjunction with the marker-less algorithm to evaluate three dimensional translations and rotations in six degrees of freedom of the cup-liner-segment, in relation to the surrounding periacetabular pelvic bone. The mean condition number for the pelvic reference segment was 47 (median 34, range 16-137) and the mean numbers of markers used was 5 (median 5, range 5-8). Mean error of rigid body fitting was <0.3 mm.

Maximum Total Point Motion (mtpm) of the center of prosthesis head was used as a proxy variable for polyethylene liner wear. Head penetration into the polyethylene liner, expressed as mtpm in mm, cannot distinguish between creep, i e plastic deformation of the polyethylene without production of wear particles, and true liner wear. We assumed that head penetration during the first year was the result of the combined processes creep and wear (91, 92). The amount of head penetration between the first and second year after surgery was considered to be solely a result of abrasive polyethylene wear. The mean condition number for the cup reference segment was 26 (median 25, range 18-43) and the mean numbers of "markers" used was 5 (median 5, range 5-8). Mean error of rigid body fitting was less than 0.3 mm.

At 12 months follow-up we did duplicated RSA-examinations in all the patients. By multiplying the standard deviation of the differences between the duplicated examinations with the appropriate t-value we obtained the 99% precision interval.

FIG 17. *All data were analyzed using the UmRSA® computer software (RSA Biomedical AB, Umeå, Sweden)*

Dual Energy X-ray Absorptiometry (DEXA)

Periprosthetic bone remodelling is a key subject in this thesis. To obtain accurate and reliable measurements of the dynamics of bone mineral density (BMD) changes after THA, we have used DEXA measurements in this thesis. DEXA quantifies bone mineral content per area and thus the entity is expressed in gram/cm2. The method is a low energy radiation technique which emits gamma irradiation with two different frequencies. After passing through the body the digital detector produce a signal for each frequency. The difference in attenuation coefficient for soft tissues, as opposed to bone of various densities, is used to calculate BMD (Fig. 18)

To achieve highly accurate and reproducible measurements, in consecutive examinations, it is important to standardize the routines with regard to the set up and the periprosthetic area to be evaluated. Patients were scanned supine with foot positioning support to get reproducible internal hip rotation (122). Apart from this, the accuracy of the DEXA machine itself was controlled by a physicist, who performed weekly scans on an aluminum vertebrae phantom. In addition to this, daily scans of a phantom were done to calibrate hardware and software parameters and radiation dose, according to the manufacturer´s guidelines. The standard deviation of the quality control values have been less than 1% of the mean since the equipment was installed at our department. In this thesis, two different DEXA machines were used. In study II we used a DPX-L™ from Lunar Co., Madison, Wisconsin, USA and in studies III-V we used a Lunar Prodigy Advance machine from General Electric Healthcare. The latter machine was used together with the software enCore version 13.31.016.

STUDY II

In study II the BMD analysis was a cross-sectional comparison of the femoral periprosthetic BMD in the operated hip, with the contralateral healthy hip as control (123, 124). On the basis of density changes between the prosthesis stem and the surrounding bone, a prosthesis mask was simulated by the software. By superimposing the mask on the healthy hip side this could be scanned at the corresponding level and BMD in seven regions of interest (ROIs), based on

Gruen's zones (125), were analyzed. The values were measured as areal BMD, g/cm2 and the ratio between the operated side and the control side was calculated and expressed in percent.

STUDY III, IV, V

In studies III-V the BMD analyses were longitudinal, i. e. a baseline value was measured postoperatively for each patient and all follow-up measurements were compared to this value. In study III we used Gruen's zones for BMD analysis. Each patient´s individual regions of interest (ROI) were saved and used for subsequent examinations to reduce measurement errors.

In study IV the Gruen´s zones differed in size between the two stem types because of the difference in stem lengths. For the ultra short stem we therefore analyzed Gruen´s zones 1 and 2 as one zone and compared it to zone 1 in the conventional stem (Fig. 19).

In study V BMD was measured in four zones defined by Wilkinson et al (126) and subsequently slightly modified by Laursen et al (127) (Fig. 20). In a study by Wilkinson et al the four-ROI method was found to be more sensitive to detect BMD changes over time than the three-ROI method originally described by DeeLee and Charnley (126, 128).

In studies III-V the change in bone mineral density in each zone was calculated by dividing the bone mineral density value from each examination by the baseline value measured two days postoperatively. The ratio was expressed as a percentage of the baseline value.

PRECISION OF DEXA

In study IV and V we performed duplicated examinations with repositioning of the patient to calculate the precision of the DEXA measurements at the 12 months follow-up. Precision was expressed as the Coefficient of Variation, in percent, i e the standard deviation of the differences between all the duplicated examinations was divided by the mean of all the mean values of the repeated examinations. The precision for each ROI is listed in (Table 7) and (Table 8). Precision was in accordance with what other research groups have reported (124, 129).

GENERAL BONE MASS EVALUATION

In studies III-V we measured every patients general bone mass at inclusion and after 2 years, to evaluate each patient´s loss in general bone mass during the study period. We scanned the proximal femur and the lumbar vertebraes, L1-L4, according to the criteria of World Health Organization (WHO total hip and WHO lumbar spine).

Clinical Outcome measures

In all the studies included in this thesis each patient's functional capacity was graded according to Charnley´s classification (130). This is a classification system for assessing the walking ability of patients who are candidates for hip arthroplasty surgery. Classification (A) denotes a patient with unilateral hip disease or unilateral THA, (B) is a patient with bilateral hip disease (or with a THA in one hip and disease in the other) and (C) is a patient with other disabilities than the hip interfering with their functional capacity such as rheumatoid arthritis, knee OA, spinal stenosis, cardiovascular or respiratory disability. This classification system allows comparison of THA results between different groups of patients. In study I-II classification was done at the time of follow-up and in study III-V it was done at the time of inclusion.

Clinical outcome was evaluated with self administered score protocols. To evaluate hip function, Harris Hip Score (HHS)(131) was used in study I-V and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (132, 133) was used in study IV-V. In study III-V preoperative assessment

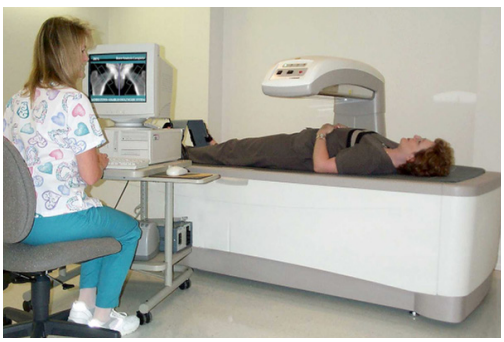


FIG 18. *Patient is scanned supine with foot supports to increase reproducibility between consecutive examinations*

Methods

was filled in at the time of inclusion, as a baseline value, and thereafter clinical outcome assessment was done at every consecutive follow-up. HHS is the most commonly used hip-specific outcome score and has been shown to be a valid and reliable score for hip function after THA (134). It consists of four domains, pain, function, hip range of movement and hip deformity. Maximum score is 100 points. Pain and function have heaviest weight accounting for 44 and 47 points respectively. WOMAC has three domains, pain, stiffness and function. Maximum points are 96. We have used a normalized WOMAC score by converting the scale to a maximum of 100 points, as is done in the National Joint Registry in England (135).

Mid-thigh pain was graded simply by asking the patients if they had mid-thigh pain or not. It was graded as none, mild, moderate or severe.

Health-related quality of life was evaluated with EQ-5D (136) in studies III-V. It is a standardized, self-reported, non-disease-specific instrument for measurement of health-related quality of life that was developed by the EuroQoL group. EQ-5D describes health status in 5 dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each dimension is divided into 3 levels: 1 - no problems, 2 – some problems and 3 - extreme problems. This generates 243 different "health states" and the EQ-5D index score assigns each "health state" a value, ranging from -0.59, indicating the worst possible health state, to a value of 1, indicating full health. EQ-5D has been used in clinical trials in many different fields of medicine and is frequently used to assess quality of life after THA (137, 138).

Statistics

The statistical analyses in this thesis have been performed with the statistical software SPSS, version 20-22, from IBM. Microsoft´s Excel 2007 has also been used.

Statistical significance was assumed at p-values <0.05.

In studies III-V, if subjects had missing data at any of the follow-ups, we used "last observation carried forward" before the calculations were done. We also re-calculated the analyses, with the data missing, and found no differences in the results.

From a study on risk prevention of hip fractures

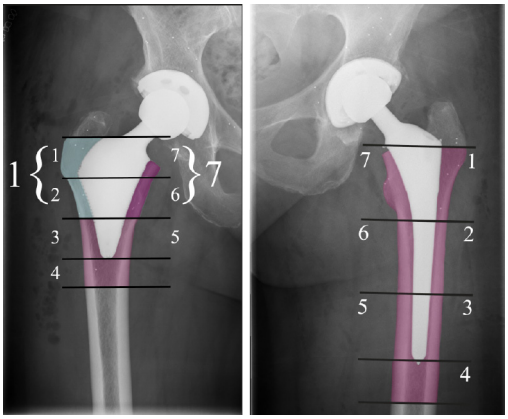


FIG 19. *Because of the difference in stem lengths Gruen´s zones 1 and 2 in the ultra short stem was analyzed as one zone and compared to zone 1 in the conventional stem. Of the same reason zones 6 and 7 were compared to zone 7 in the conventional stem By doing so the proximal zones in both stems were anatomically comparable and easily reproducible. Photo by Carin Wesström*

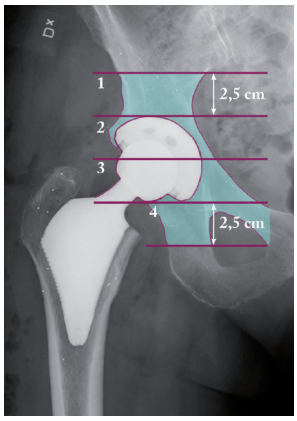


FIG 20. *Bone mineral density was measured in four zones defined by Wilkinson and subsequently slightly modified by Laursen. Photo by Carin Wesström*

TABLE 7. ***Precision of Dexa measurements in all Gruen zones calculated with Coefficients of variation in percent (CV%).***

Gruen zone	1*	2**	3	4	5	6**	7*
CV%	5.5	3.3	4.7	2.8	4.1	2.7	7.0

*** For the ultra-short stem Gruen zone 1 and 2 are analyzed together as zone 1 and zone 6 and 7 are analyzed as zone 7. **Only the results for the conventional stem are shown.**

TABLE 8. ***Precision of Dexa measurements in the four periacetabular zones calculated with Coefficients of variation in percent (CV%).***

Zone	1	2	3	4
CV%	2,9	4,4	5,6	4,5

Methods

with bisphosphonate treatment, a BMD increase of approximately 5% in the proximal femur was found to reduce the relative risk with 70% (absolute risk reduction 1.1%) (49). In the power analyses we therefore assumed that a difference in BMD of 10-15% would be clinically relevant in preventing future periprosthetic fractures.

Bone remodelling data and stem migration data were tested for normality and homogeneity using Kolmogorov-Smirnov and Levene´s test.

Clinical score data were analyzed with non-parametric Mann Whitney U-test for between group comparisons since these are ordinal data level.

In studies IV-V correlations between change in bone mineral density and other factors known to influence BMD, such as age, gender (26, 139), BMI (140, 141) and preoperative general bone mass were analyzed with a multivariate linear regression analysis.

STUDY I AND II

The Mann-Whitney U-test was used to test the association between HHS and Charnley´s classification system.

Even though functional score data are on ordinal data level we presented mean HHS values because this is how it is often presented in scientific journals.

In study II, Pearson´s correlation coefficient was calculated to illuminate the relationship between BMD-loss and time from surgery to follow-up.

STUDY III

Analyses of efficacy with risedronate treatment compared to placebo were based on the intention-to-treat principle. All patients that received at least one dose of the study drug were included in the final analyses.

A power analysis, with the above mentioned assumption for a clinical relevant increase of BMD as a basis, showed that a total of sixty patients (thirty in each group) would be required to provide 90% power to detect a difference of 10% in BMD in zones 1 and 7, assuming a standard deviation of 11% (142) and considering a two-sided p-value of 0.05 to be significant. We therefore planned to recruit seventy-four patients to allow for losses.

Differences in BMD between the two groups, at each follow-up, were analyzed with independent student´s t-test.

We used a one-way repeated measures analysis of variance (ANOVA) to detect an overall effect of treatment throughout the study period. Factors known to influence periprosthetic bone loss, such as sex (139), age, BMI (140), stem size (142) and pre-operative BMD in the hip (33), were included as covariates in the analyses.

A subgroup analysis of changes in periprosthetic BMD, in subjects dichotomized to either having high or low preoperative bone mass based on the median BMD in the hip preoperatively, was performed.

STUDY IV

A power analysis revealed that to detect a difference in BMD of 15%, in Gruen zones 1 and 7, with a power of 90%, on a 5% significance level, 17 patients were required in each group, if the standard deviation was 14%. To add up for possible drop outs we included 25 patients in each group.

Bone mineral density data were normally distributed but point motion radiostereometric data regarding stem migration were not. Between groups comparisons were analyzed with independent student´s t-test for BMD data and with Mann-Whitney U-test for implant migration data. With-in groups longitudinal BMD changes were analyzed with paired t-test.

Presence or absence of the clinical outcome parameter "mid-thigh pain", in the two groups, was analyzed with chi-square test, and Fischer´s exact test, due to observations being fewer than five.

STUDY V

A power analysis revealed that to detect a difference in BMD of 10%, proximal to the cup in ROI 1 and 2, with a power of 90%, on a 5% significance level, 22 patients were required in each group, if standard deviation was 10% (126, 141). To account for possible drop outs we included 25 patients in each group.

Both bone remodelling data and implant migration data were normally distributed. We used independent student´s t-tests for between group comparisons.

Results

9 RESULTS – SUMMARY OF PAPERS

Study I

We retrospectively evaluated 60 patients (62 hips) after femoral revision due to aseptic loosening with a proximally porous and hydroxy-apatite coated uncemented tapered titanium stem. Surgery was performed between 1989 and 2002. Bone defects at revision were small to moderate. We found a good clinical outcome, a stem survival rate of 95% (95% CI: 0.83-0.98) and obvious signs of stress shielding after a mean follow-up of 6 years.

CLINICAL OUTCOME

Mean HHS at follow-up was 75 (range 30-100). Almost half of the patients were classified as Charnley functional class C. We noted lower HHS for patients in this function class compared to patients in class A ($p < 0.001$) and B ($p < 0.005$) (Fig. 21)

RADIOGRAPHICAL OUTCOME

Bone defects prior to revision surgery were mostly of grade I and II in the Gustilo-Pasternak classification and of grade II and III in the Endo-klinik classification. The latter classification being more sensitive to smaller bone defects than the former. In nineteen stems we suspected subsidence, but with plain radiography a migration larger than 4 mm is required for a change in position to be valid (108). Five stems had subsided with certainty, with a maximum distance of 8 mm. At follow-up, all stems were well osseointegrated. Several skeletal signs of fixation were seen indicating stem ingrowth both proximally and distally. Obvious signs of stress shielding were present (Table 9).

COMPLICATIONS

Nine patients had dislocations, and 2 of these were recurrent (Table 10). The incidence of dislocation was higher than in other comparable studies (18). We had four peroperative calcar fissures and four postoperative periprosthetic fractures. This compares favorably to other studies using proximally coated prosthesis in femoral revision (143, 144).

TABLE 9. ***Bone remodelling at follow-up (53 hips)***

STEM STABILITY PARAMETERS	No.
Fixated stems	53
Subsidence	19
Change in varus-valgus alignment	0
Spot welds	30
STRESS-SHIELDING PARAMETERS	
Calcar resorption	16
Calcar "round-off"	7
Distal cortical hypertrophy (1-4 mm)	14
BONE REMODELLING PARAMETERS	
Osteolysis at revision	48
Regression of osteolysis	
total	7
partial	37
Newly formed osteolysis	2
UNSPECIFIED PARAMETERS	
Pedestal formation	36
Reactive lines	16
Heterotopic ossification	
grade 1/2/3/4	13/6/5/0

TABLE 10. ***Complications and revision surgery of the original 62 hips***

Complications	n	Stem re-revision	Cup revision/liner exchange
Dislocation[a]	9		1
Cup loosening	5		5
Periprosthetic fracture			
Peroperative[b]	4	1	
Postoperative	4	2[c]	
Deep infection	1		
Superficial infection	2		
DVT	1		
Sensory sciatic nerve injury	1		

[a] Two had recurrent dislocations, 1 underwent liner exchange converting it to a larger articulation.

[b] Two of these were treated with cerclage wiring peroperatively. The revised patient, who sustained a fissure in the lesser trochanter peroperatively, suffered from pain and subluxations. The stem had subsided and he was re-revised using impacted morselized bone allograft and a cemented stem.

[c] One re-revision due to fracture through a fenestration done at surgery and one after a fall 18 months after surgery.

Results

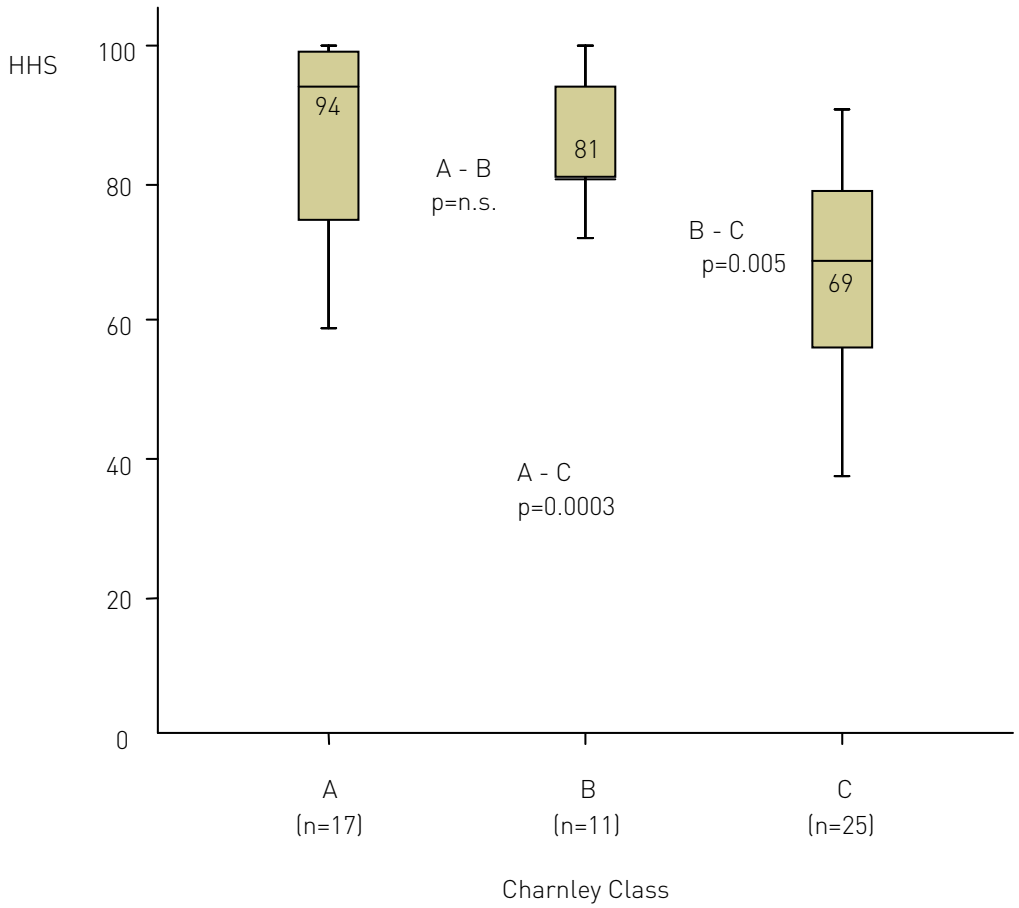


FIG 21. *Harris hip score (HHS) in the different Charnley classes (A, B, C) Significance between groups measured with Mann-Whitney U test.*

Results

Study II

We found a pronounced reduction of periprosthetic bone mineral density (BMD) in all Gruen zones (125) compared to the contralateral healthy hip 6 years after uncemented aseptic femoral revision with a proximally porous and hydroxy-apatite coated tapered stem. Most pronounced bone loss was registered in the proximal zones, both medially and laterally, where BMD had diminished with 36-45%.

Patients in study II are a subgroup of patients from study I. To ensure similar conditions for bone metabolism we only included patients who had had their first THA because of primary osteoarthritis. The cohort consisted of 22 patients who had undergone uncemented femoral revision due to aseptic loosening and had a healthy hip on the contralateral side. In 13 of the 22 (59%) patients proximal impaction of small amounts (10-20 ml) of morselized bone grafts was performed to fill out the gap between the stem and the endocortices.

After a mean of 6 years following surgery, we retrospectively reviewed the patients clinically using Harris Hip Score (HHS), and radiograhically regarding stem fixation and skeletal signs of bone remodelling, according to Engh´s fixation score (107). Periprosthetic bone mineral density (BMD) was evaluated with DEXA.

TABLE 11. ***Bone remodelling at follow-up (22 hips)***

STEM STABILITY-PARAMETERS	No.
Fixed stems	22
Subsidence (5- 7 mm)	2
Change in varus-valgus alignment	0
Spot welds	12
STRESS SHIELDING-PARAMETERS	
Calcar resorption	8
Calcar "round off	2
Distal cortical hypertrophy (1-4 mm)	6
BONE REMODELLING- PARAMETERS	
Osteolysis at revision	21
Regression of osteolysis	19
Newly formed osteolysis	1
UNSPECIFIC PARAMETERS	
Pedestal formation	16
Reactive lines	7
Heterotopic ossification grade 1/2/3/4	6/2/1/0

CLINICAL AND RADIOLOGICAL OUTCOME

Mean HHS at follow-up was 74 (median 73, range 30-100). For patients in Charnley functional class A (n=13) mean HHS was 86 points and for those classified as class C (n=9) it was 58. The difference was statistically significant (p = 0.003).

It has already been mentioned that all stems were well fixed. Bone remodelling parameters revealed signs of stress shielding, similar to those in study I (Table 11).

BONE MINERAL DENSITY CHANGES

The median change in periprosthetic BMD was expressed as a percentage of that on the healthy side for each of the 7 zones. Bone loss around the stem was pronounced and the difference between the sides were statistically significant (p<0.05) in every zone (Fig. 22). We could find no association between BMD loss and grade of bone deficiency at revision, time elapsed from surgery to follow-up or patients that had been bone grafted proximally compared to those who had not.

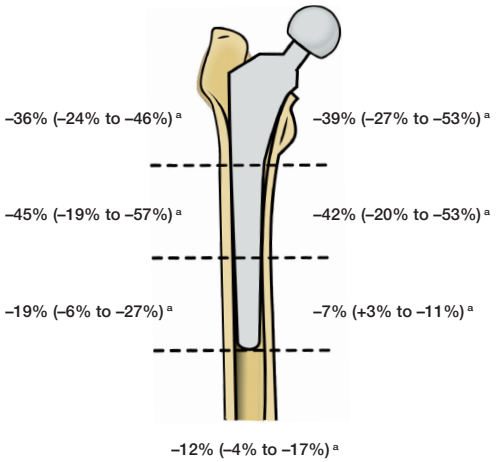


FIG 22. *Percentage side difference in BMD in different Gruen regions after the rearthroplasty. Median values (25–75 percentiles) are given. An asterisk indicates a difference between sides (p < 0.05).*

Results

Study III

In this prospective randomized, double-blind, placebo-controlled trial of 73 patients with primary hip osteheoarthritis, 35 mg of risedronate, taken orally, once weekly, was effective in reducing periprosthetic femoral BMD resorption up to one year after surgery. There was a trend towards an effect up to 2 years. No effect on stem migration or clinical outcome was seen.

CLINICAL OUTCOME

Clinical outcome evaluated with HHS, EQ-5D and Pain Numerical Rating Scale (PNRS) showed equally excellent improvements in both groups with no statistically significant differences. Improvements in HHS (median values) were 45 to 100 versus 48 to 98 in the Risedronate and placebo group respectively (p=0.134)

RADIOLOGICAL OUTCOME

Bone remodelling and stem fixation was evaluated according to Engh´s fixation and stability score (107). All stems were stable. Using Einzel-Bild-Roentgen-Analyse (EBRA) (110, 111) a mean vertical stem subsidence of 1.7 mm (SD 1.2-1.5) in both groups was recorded two years after surgery.

BONE MINERAL DENSITY CHANGES

Periprosthetic BMD was measured with DEXA in the seven regions described by Gruen (125). The first postoperative examination, 2 days after surgery, served as baseline. Each consecutive examination was correlated to this and the ratio was expressed as a percentage. Dexa examinations were performed at 3, 6, 12 and 24 months after surgery. BMD resorption was significantly reduced in the risedronate group, up to 2 years after surgery, when repeated measure analysis of variance (ANOVA) was used to compare the two groups. However, when difference in BMD, between the groups, at each follow-up was compared with student´s t-test, BMD loss was significantly less in the risedronate group up to 6 months in zones 1 and 7, and it stayed significantly reduced at 12 months in zone 1 (Table 12). After cessation of bisphosphonates, 6 months after surgery, BMD diminished faster in the risedronate group than in the placebo group and, as is shown in (Fig. 23), differences in BMD were no longer statistically significant.

COMPLICATIONS

Adverse events were evenly distributed in the two groups (risedronate group 20/36 patients, placebo group 24/37 patients, p=0.416). One patient was revised shortly after surgery because of a dislocation. Four patients in the risedronate group discontinued the study drug because of urticaria (2) and nausea (2). None in the placebo group did the same (p=0.037). Two patients withdrew their informed consent, but were followed clinically and radiologically. One of these had nausea postoperatively, the other experienced no adverse events.

We had one pulmonary embolus and one deep vein thrombosis, both in the placebo group.

TABLE 12. ***The effect of risedronate on BMD***

Outcome	risedronate	placebo	difference (95% CI)	p value
CHANGE IN BMD ZONE 1 (%)[a]				
3 months	1.2±7.6	-5.9±9.0	7.2 (3.2 – 11.1)	<0.001
6 months	-0.5±10.8	-9.7±9.9	9.2 (4.2 – 14.1)	<0.001
12 months	-7.4±14.7	-14.5±11.2	7.2 (1.0 – 13.3)	0.006
24 months	-13.6±12.3	-17.7±13.1	4.1 (-2.0 – 10.2)	0.066
CHANGE IN BMD ZONE 7 (%)[a]				
3 months	-3.6±10.2	-10.3±10.9	6.7 (1.6 – 11.7)	0.007
6 months	-5.1±10.6	-13.1±11.7	8.0 (2.7 – 13.4)	0.003
12 months	-11.9±12.3	-16.1±12.0	4.3 (-1.5 – 10.1)	0.318
24 months	-17.2±13.2	-18.1±14.9	0.9 (-5.9 – 7.7)	0.699

[a] mean ±SD, p-value Student's t-test.

Results

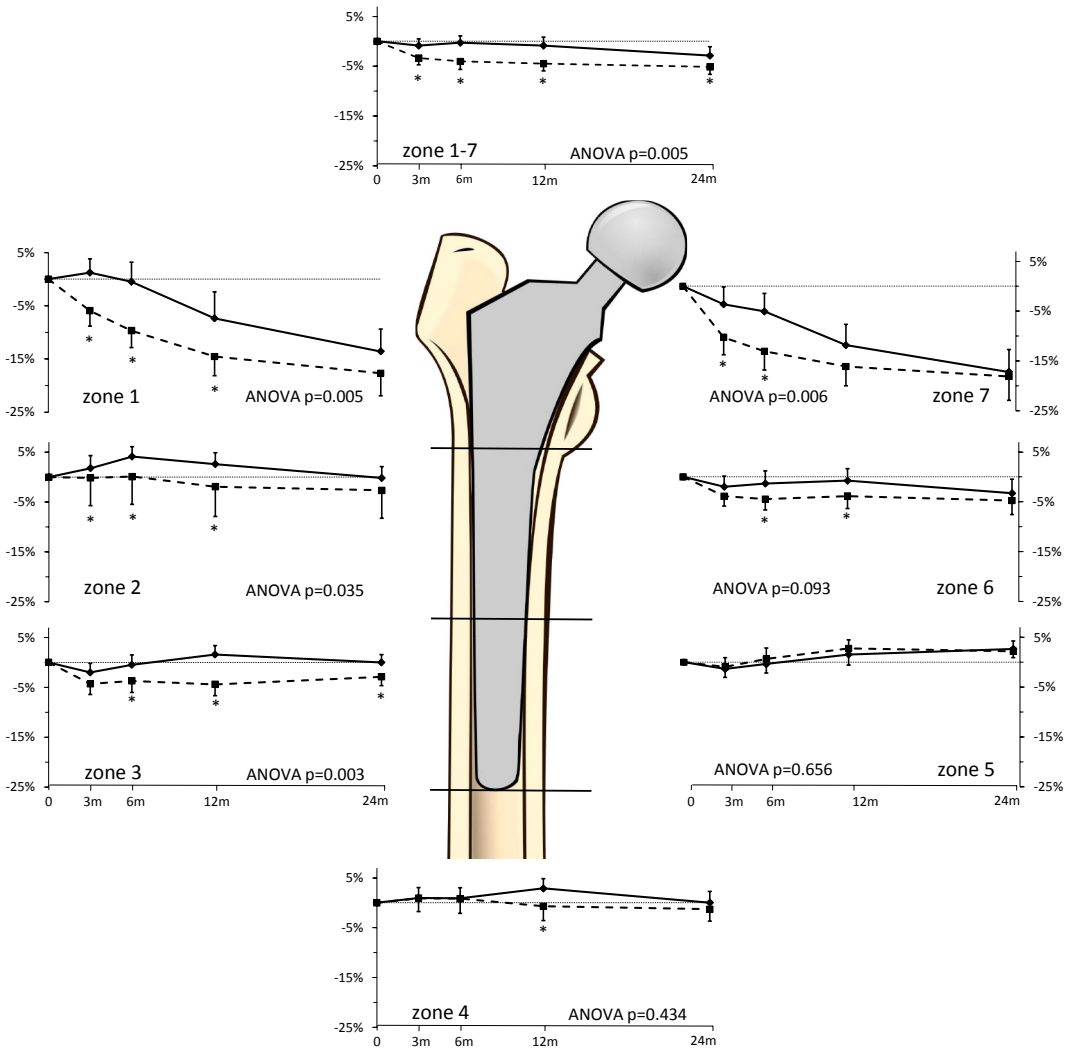


FIG 23. *The mean (95% CI) percentage change in BMD around the stem in patients receiving risedronate (solid line) or placebo (dashed line). *p≤0.05.*

Results

Study IV

In this prospective randomized controlled trial 51 patients with primary hip osteoarthritis were randomized to uncemented THA with an ultra-short stem or a conventional tapered stem. The ultra-short stems had less BMD loss compared to the conventional stems up to 2 years after surgery. Stems in both groups became well fixed and the clinical outcome was equally excellent.

CLINICAL OUTCOME

There was a trend for larger improvement in clinical scores in the ultra-short stem group but no statistically significant differences were seen. Improvements in HHS were 46 to 95 for the ultra-short stems versus 56 to 92 for the conventional stems (p=0.173). Improvements in the WOMAC score were 43 to 95 versus 46 to 95 for the ultra-short stems and the conventional stems respectively (p=0.085), (median values). During the first 6 months there were more patients suffering from mid-thigh pain in the conventional stem group, but the differences were not statistically significant at any time. One patient in each group was excluded from the analyses because of a periprosthetic fracture and a periprosthetic infection respectively.

BONE REMODELLING

Periprosthetic femoral BMD was evaluated with DEXA post operatively and at 3, 6, 12 and 24 months after surgery (Fig. 24). Because of the difference in stem lengths the Gruen´s zones differed in size between the two stem types. For the ultra short stem we therefore analyzed Gruen´s zones 1 and 2 as one zone and compared that to zone 1 in the conventional stem. For the same reason, zones 6 and 7 were analyzed as one zone and compared to zone 7 in the conventional stem (Fig. 19). The ultra-short stems had less BMD loss at every follow-up except for in Gruen zone 7 at 24 months (Fig. 25). For the conventional stems longitudinal bone loss from baseline to 24 months after surgery was statistically significant in all three measured regions, i e Gruen zones 1, 7, 1-7. For the ultra-short stems a statistically significant longitudinal reduction in BMD was only seen in zone 7 during the same period.

IMPLANT MIGRATION

To compare migration of the two stem types we measured Maximum Total Point Motion (mtpm) with radiostereometry (RSA). According to published guidelines for reporting RSA results (121), mean error of rigid body fitting was set to <0.3 mm and cut off limit for condition number to <120. Precision for our set up was 0.54 mm. The ultra-short stems migrated 0.77 mm more during the first six weeks (p=0.002). From six weeks to 24 months migration was 0.2 mm and 0.13 mm for the ultra-short and the conventional stems respectively (p=0.861). Three months after surgery no further migration was seen and all implants were stable (Fig. 26).

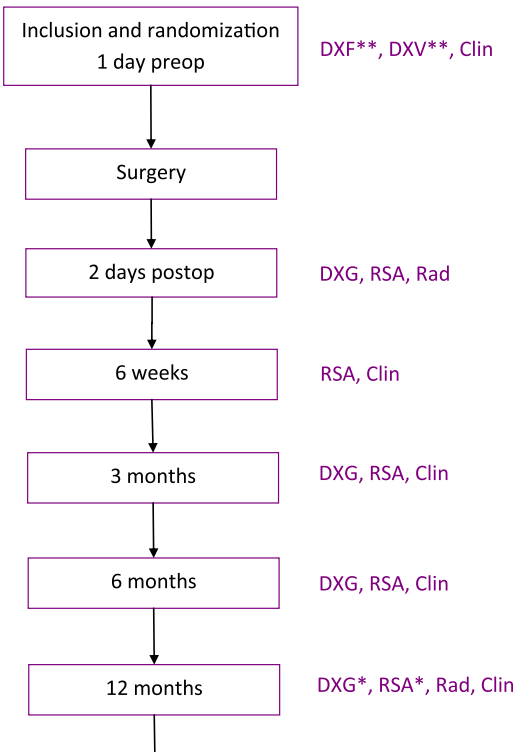


FIG 24. *Follow-up protocol in study IV*
*DXG= Dexa scan of Gruen zones, DXF=Dexa scan of proximal femur (WHO total hip), DXV= Dexa scan of vertebrae L1-L4 (WHO Lumbar spine), RSA=Radiostereometry radiographs, Rad=Anterioposterior and lateral radiographs, Clin=Self-administered clinical scores including HHS, WOMAC, EQ-5D. *Duplicated examinations for calculating precision*
***General bone mass evaluation*

Results

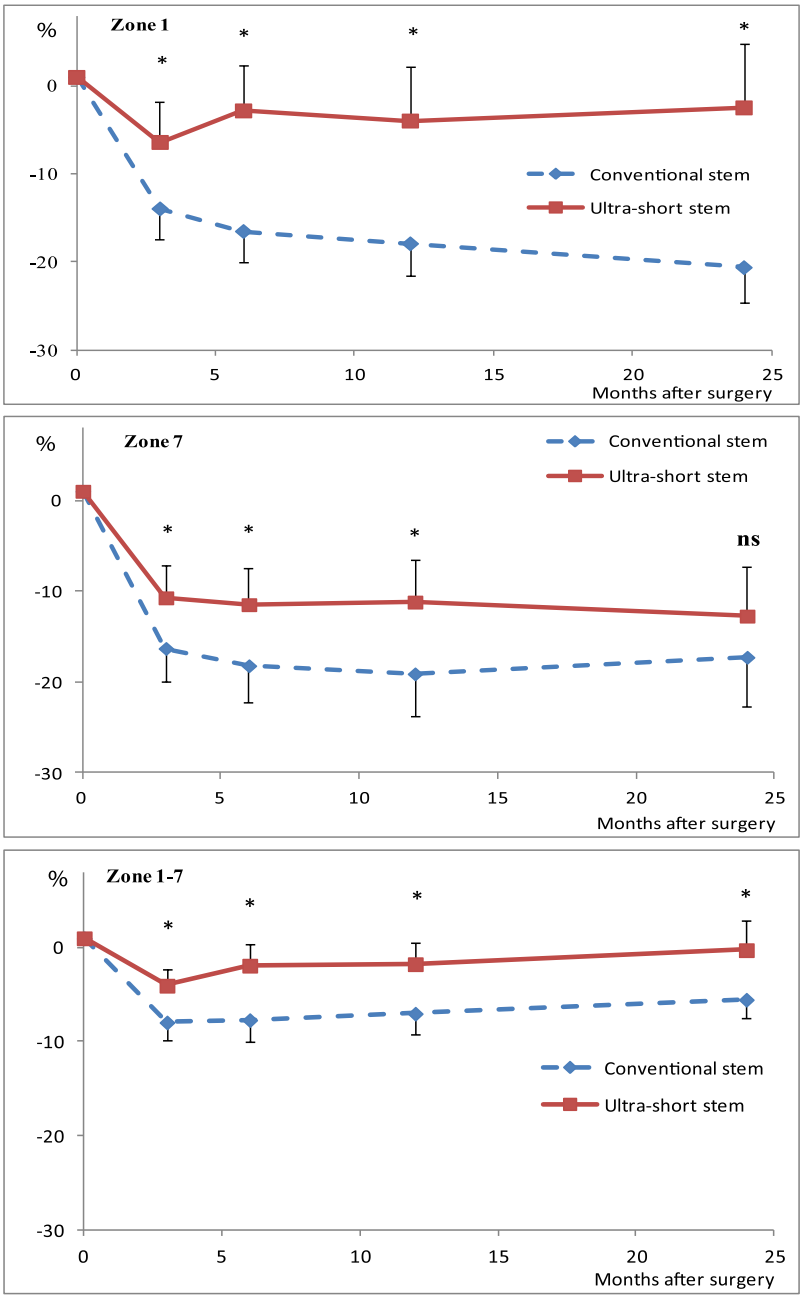


FIG 25.
Mean percentage change in bone mineral density in Gruen zones 1, 7, 1-7. Error bars 95% CI. Differences analyzed with Independent student´s t-test, p<0.05. **ns** *= non significant difference.*

Results

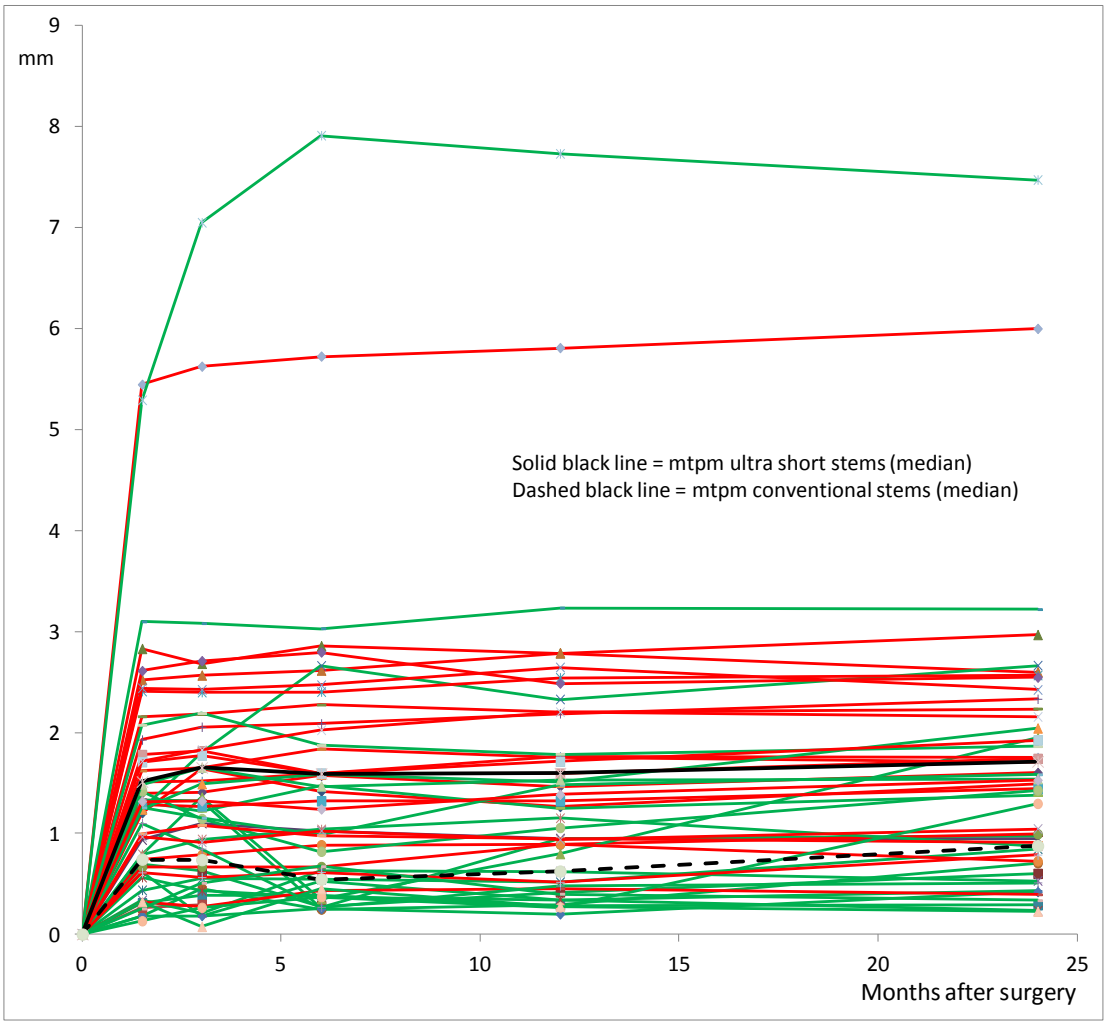


FIG 26.
Stem migration as maximum total point motion (mtpm) in millimeter for individual stems. Red lines for ultra-short stems, green lines for conventional stems.

Results

Study V

In this prospective randomized controlled trial 51 patients with primary hip osteoarthritis were randomized to uncemented THA with either an acetabular titanium cup with a three dimensional porous titanium construct backside, together with an α-tocopherol-treated highly cross-linked ultra high molecular weight polyethylene (HXLPE) liner, or a porous and hydroxyapatite coated conventional titanium cup with a +4 mm offset HXLPE liner.
No differences in periacetabular bone remodelling, implant fixation or polyethylene liner wear was found up to 2 years after surgery. However, creep was significantly less in the α-tocopherol-treated liner. Both implants conserved the periacetabular bone and the clinical outcome was equally excellent.

CLINICAL OUTCOME

Patients in study V were also included in study IV in this thesis. No statistically significant differences between the groups were seen in clinical outcome, measured with HHS, WOMAC and EQ-5D. Improvements in HHS were 56 to 92 points for the porous titanium construct cups and 46 to 95 for the conventional cups (p=0.173) (median values). WOMAC score improved from 46 to 95 versus 43 to 95 points (p=0.085) (median values), for the porous titanium construct and conventional cups respectively. One patient in each group was excluded from the analyses because of a periprosthetic femoral fracture and a periprosthetic infection respectively.

BONE REMODELLING

Periacetabular BMD was evaluated with DEXA in four zones described by Wilkinson et al (126) and Laursen et al (127), (Fig. 20). Dexa examinations were performed postoperatively and at 3, 6, 12 and 24 months after surgery. Comparison of bone remodelling in the periacetabular region as an entity, i e zones 1-4, showed that bone mineral density was almost completely restored to baseline values after 24 months in both groups (Fig. 27). The pattern of bone remodelling was also similar in the two groups, with diminishing BMD in the two proximal zones and increasing BMD in the two distal ones. There was a trend for less bone loss in the zones behind the porous titanium construct shell, i e zones 2 and 3, compared to corresponding zones behind the conventional shell.

IMPLANT MIGRATION

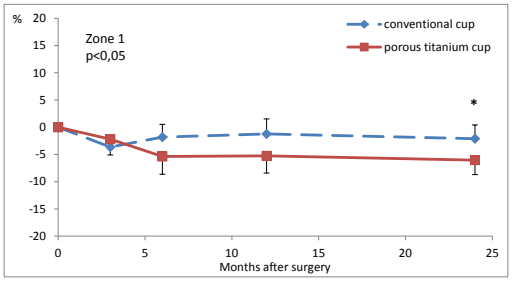
Radiostereometric analysis revealed an initial micromotion in both implants up to 6 months postoperatively. After that, all implants were stable and we saw no radiographic signs of loosening. The porous titanium construct cup migrated 0.14 mm (95% CI -0.28 to -0.0005, p=0.049) more proximally than the conventional cup did. Apart from this, differences in shell migration in all six axes were non-significant at all follow-ups (Table 13).

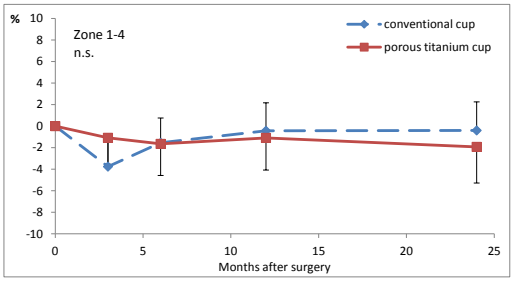
POLYETYLENE WEAR

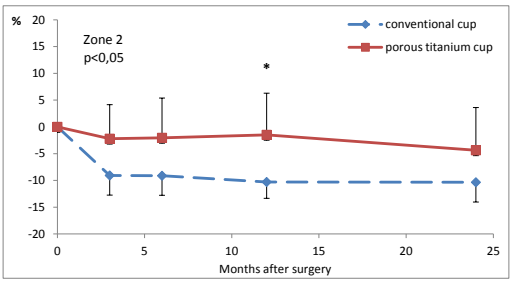
Maximum Total Point Motion (mtpm) was used as a proxy variable for polyethylene liner wear. The difference in head penetration between the two polyethylene liners was statistically significant up to 12 months after surgery. Less head penetration was measured for the α-tocopherol-treated liner, (Fig. 28). However, at 24 months the difference was 0.07 mm (95% CI -0.001 to 0.15) which was non-significant (p=0.090).

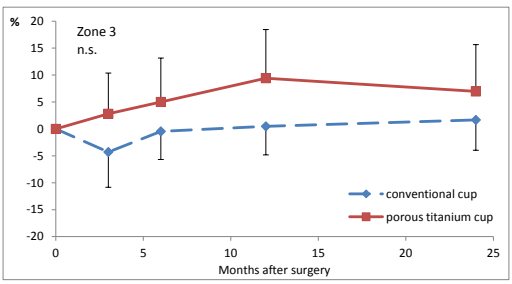
We assumed that head penetration during the first year was the result of the combined processes creep and wear (88, 89). Polyethylene wear rate, expressed as the amount of head penetration between the 12 months examination and the 24 months examination, was 0.031 mm/year (SD±0.12) and -0,003 mm/year (SD±0.08) for the α-tocopherol treated liner and the conventional liner respectively. The difference -0.033 mm/year (95% CI -0.09 to 0.02) was not significant (p-value 0.236).

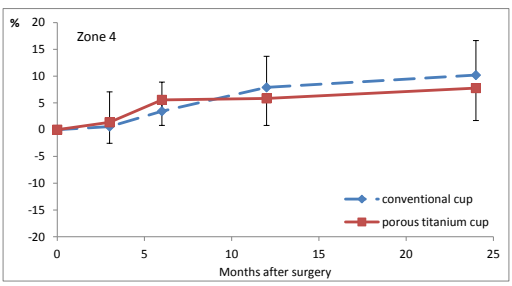
Results











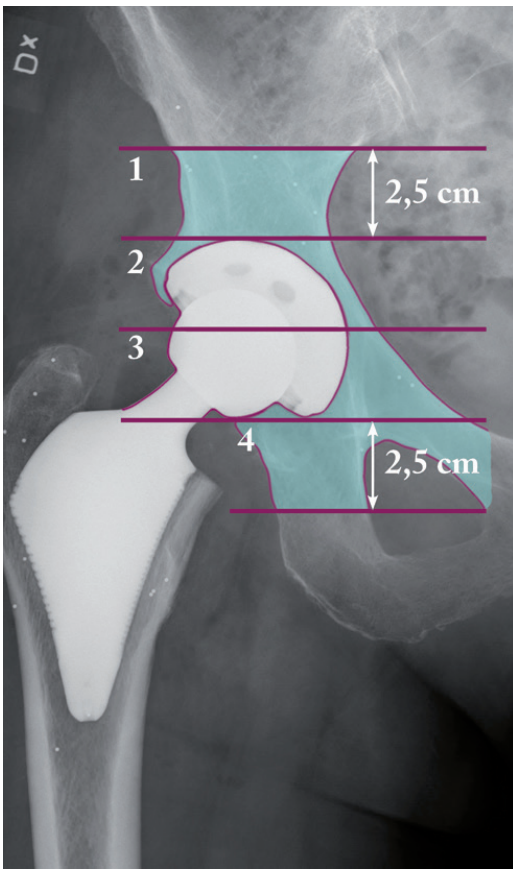


FIG 27. *Mean percentage change in bone mineral density in zones 1, 2, 3. 4 and 1-4. Error bars 95% CI. Differences analyzed with Independent student´s t-test, p<0.05. n.s. = non significant differences. Photo by Carin Wesström*

Results

TABLE 13. *Total migration 24 months after surgery and differences in cup migration in six degrees of freedom at each follow-up measured with radiostereometry (RSA).Conventional cup in relation to porous titanium construct cup.*

		X-rotation†	Y-rotation†	Z-rotation†	X-translation‡	Y-translation‡	Z-translation‡
6 weeks	Difference	-0.76	-0.63	0.01	-0.03	-0.13	0.08
	95% CI	-1.61-0.10	-1.75-0.48	-0.60-0.62	-0.18-0.13	-0.25 - -0.02	-0.06-0.23
	p-value	0.081	0.260	0.964	0.732	0.024	0.259
3 months	Difference	-0.85	-0.63	0.06	-0.03	-0.14	0.03
	95% CI	-1.81-0.11	-1.78-0.52	-0.56-0.68	-0.18-0.12	-0.25- -0.02	-0.13-0.20
	p-value	0.081	0.277	0.855	0.682	0.022	0.679
6 months	Difference	-0.50	-0.60	0.01	-0.06	-0.16	-0.08
	95% CI	-1.40-0.40	-0.90-0.71	-0.63-0.64	-0.22-0.11	-0.28- -0.05	-0.22-0.05
	p-value	0.268	0.365	0.986	0.489	0.006	0.226
12 months	Difference	-0.57	-0.18	-0.11	-0.07	-0.16	-0.02
	95% CI	-1.49-0.33	-1.44-1.08	-0.72-0.51	-0.23-0.10	-0.29- -0.02	-0.19-0.01
	p-value	0.210	0.776	0.727	0.438	0.025	0.772
24 months	Difference	-0.92	-0.45	-0.04	-0.04	-0.14	-0.01
	95% CI	-1.89-0.04	-1.76-0.85	-0.72-0.64	-0.24-0.16	-0.28- -0.0005	-0.16-0.14
	p-value	0.060	0.489	0.899	0.682	0.049	0.902
Total migration	Porous titanium cup	1.8±1.8	1.7±2.5	-0.4±1.1	0.09±0.40	0.38±0.27	-0.10±0.31
	Conventional cup	0.9±1.5	1.3±1.9	-0.5±1.2	0.05±0.30	0.24±0.21	-0.11±0.21

† degrees, ‡ millimeter

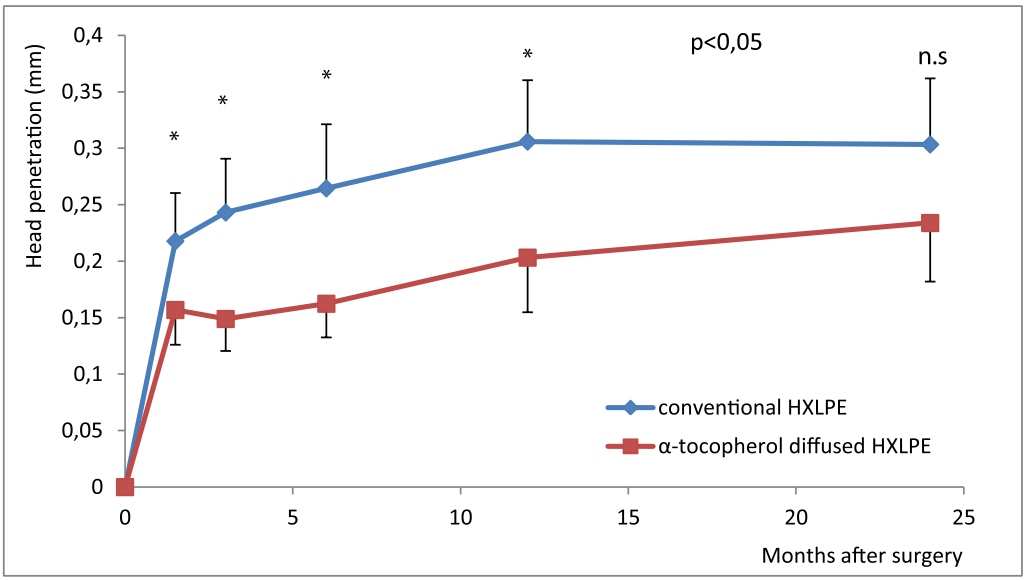


FIG 28. *Head penetration into the articulating polyethylene as a result of creep and wear. Error bars 95% CI. n.s. = non significant difference. Differences analyzed with Independent student´s t-test.*

10 DISCUSSION

10.1 DISCUSSION ON MATERIAL

The Bi-Metric stem

We have used the Bimetric stem in uncemented THA for 24 years at our institution. The long term outcome has been excellent with a survival rate of 100% for aseptic loosening (145). Even though the stem is designed for metaphyseal fixation, osseointegration occurs both proximally and distally leading to obvious signs of distal load transfer (142, 145). The Bimetric stem we used has porous- and HA-coating proximally, but there are numerous studies showing equally excellent long term stem survival with and without HA proximally (Table 14).

TABLE 14. *Studies on the uncemented Bi-Metric stem with and without HA-coating. Only studies with a minimal follow-up of 5 years of 50 hips are shown. In the bottom is, for comparison, the unpublished data from Danderyds Hospital.*

Authors	year	n	age	fu (yr)	HA	aseptic loosening	all revisions
Puolakka et al.	1999	384	n.r.	7.5	no	0.8%	2.7%
Jacobsen et al.	2003	97	50	8.0	no	0%	1%
Yamamoto et al.	2003	70	55	6.8	no	0%	0%
Lybäck et al.	2004	77	28	9.6	no	0%	2.1%
Meding et al.	2004	105	56	11	no	0%	0%
Bodén et al.	2006	115	52	12.2	yes	0%	0%
Eskelinen et al.	2006	1982	<55	6.6	no	1.9%	3.7%
Isaac et al.	2007	58	57	7.6	no	0%	0%
Sköldenberg et al.	2009	332	52	12.9	yes	0%	0%
Davies et al.	2010	64	54	15.2	no	0%	0%
Mäkelä et al.	2010	5379	>55	6.8	no	1.0%	2.5%
Danderyd Hospital	2010	1718	61	7.3	yes	0%	0.8%

n: number of hips, age: mean age at surgery, fu: mean follow-up time in years

The Proxima stem

Our experience with the Proxima ultra-short stem is that it is more technically demanding than implantation of a conventional stem. During the pilot series preceeding study IV we learnt a few technical skills. The advocated "round the corner"-broaching technique, where broaching is done with successively larger broaches in an arced manner "around" the femoral calcar, is soft tissue sparing for the abductor muscles. The prolonged medial facet of the stem favors a high neck resection level which is bone conserving compared to insertion of a conventional stem (Fig. 29). It is important to be quite aggressive in sizing, especially in the AP-plane to get initial rigid press fit fixation. The wedge shape of the ultra-short stem is "blunt" enough to tolerate hard impaction without high risk of inducing femoral fractures. We had no peroperative fracture in our series. Bone quality is also a key parameter to achieve initial rigid fixation.

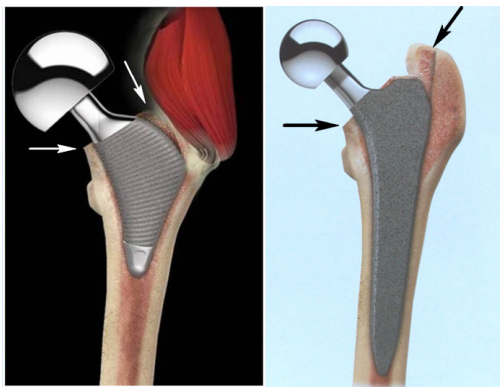


FIG 29. *Insertion of the ultra-short stem is bone conserving with a higher neck resection level and less violation of the gluteus medius muscle insertion.*

Discussion

Hydroxyapatite

The most prevalent form of inorganic bone mineral is hydroxyapatite (HA), $Ca_{10}(PO4)_6(OH)_2$, with a molar ratio of 1.67. By coating implants with calcium phosphate ceramics. a bioactive layer is introduced in the interface between metal and bone. Bioactivity is mediated via dissolution of Calcium and Phosphate ions in the interface followed by a tissue response where osteoblasts adhere to the metal surface and bone formation starts. Bone formation coupled to balanced bone remodelling, where the calcium phosphate ceramics is gradually replaced by new bone formation, will ensure a biological fixation of the metal component into the bone. Various parameters will influence the properties of the HA-coating. The most important of these are the chemical composition, i. e. the proportions of the different calcium-phosphates, the method of attachment on to the metal substrates, the cristallinity, density, purity and thickness of the ceramic layer. The level of cristallinity will determine the resolution rate of the coatings and thus, the grade of bioactivity. A more amorphous compound has higher bioactivity because of quicker resolution. On the other hand, higher cristallinity will enhance the mechanical properties, as will a thinner coating. As a rule of thumb, as high a purity as possible (95-97%), cristallinity of 70-90% and a coating thickness of 50-75µm is thought to be advantageous in a clinical setting.

In both experimental and in vivo settings HA has been shown to have an osteoconductive effect enhancing bone formation (146, 147). It has also been shown to stimulate bone formation to bridge over wider gaps between bone and implant, by inducing bone formation from the implant side of the gap as well as from the host bone tissue (65-67). The attachment strength of a HA-coated implant into the bone is increased compared to Ti-implants without HA-coating and HA has also been shown to facilitate and improve fixation of an implant in situations where micromotion is present (65, 69). Except for the mechanisms mentioned above, where HA enhances and facilitates bone ingrowth, HA has also been shown to contribute to reduced periprosthetic osteolysis. Wear debris from the joint articulation and from other sources that contribute with inflammatory agents in the local environment, such as cement particles and detached HA-particles, migrates in to the interface between the implant and the host bone. The inflammatory response to these particles from macrophages gives rise to local bone resorption known as osteolysis (40, 148, 149). This is an important mechanism for periprosthetic bone loss which eventually can lead to failure of the implant fixation. In an implant with a circumferential layer of HA the interface gets "sealed off" and the origin and progress of especially distal femoral osteolysis can be prevented (70, 71).

Technically, HA-coating of implants can be done in several ways. It is of utmost importance to get a strong adhesion to the underlying surface to prevent delamination of the HA layer. Different methods of chemical deposition have been used. A favorable method is deposition of HA by plasma-spraying it on to the metal substrate. This means injecting HA-particles in a high-temperature gas flame beamed at the metal substrate where layers of HA-particles are built up (146). More recently, other methods to adhere the HA-coating to the substrate are performed by electrochemical deposition (150, 151). With this method the HA-layer can be made much thinner (5 µm). This is thought to be advantageous from a mechanical point of view and the optimal pore size of the underlying porous coating, ~300 µm, can be preserved. Resorption of a thinner layer of HA would also be quicker which might contribute to faster bone ingrowth. In a randomized controlled trial, comparing a stem with plasma-sprayed HA to the same stem with electrochemically deposited HA, the latter was found to retain significantly more bone in Gruen zone 1 during the first 2 years. No difference in stem migration or fixation could be seen between the two groups (151).

There are concerns of side effects with HA-coating as well. The risk of delamination of the coating from the metal surface has been mentioned in Introduction. If delamination of a more substantial area of HA would occur implant fixation could be at risk. This phenomenon has been reported after HA-coating of smooth Ti cups (81, 82). Mechanically detached HA-particles can act as abrasive wear particles with deterioration of articulating surfaces and also act as inflammatory agents leading to deterioration of interface homogeneity (79, 80). In two registry studies from the Swedish Hip Arthroplasty Register these mechanisms was thought to be the reasons for the

Discussion

increased risk of cuprevision seen with HA-coated acetabular implants in a primary setting and also the reason for increased risk of liner re-revision in a revision setting (78, 152)

Polymers

Polyethylene is the most predominately used bearing surface in THA. The material consists to approximately 55% of a crystalline part and to 45% of an amorphous part. The molecule is built up by enormously long chains of carbon-hydrogen in repetitive polymers of ethylene, CH_2-units. These carbon-hydrogen chains, folding back and forth, form microscopic lamellae which build up the crystalline part of the material. Because of the long chains of polymers the molecular weight is very high which explains the technical name of this material, ultra high molecular weight polyethylene (UHMWPE).

MANUFACTURING AND STERILIZATION OF POLYETHYLENE

In principle, there are three different ways to manufacture a polyethylene cup or liner. Pressure, temperature and time are crucial parameters to influence the characteristics of different types of PE. Compression molding means that the PE is compressed directly to the final shape of the implant. Ram extrusion means that a long bar of PE is manufactured first and from this is the implant machined to its final shape. The third method is a multistep process called HIPing (hot isostatic pressure) where machining also is used to produce the final implant.

Sterilization of the polyethylene can be carried out in different ways, each with its pros and cons regarding the influence on wear characteristics of the material. Surface sterilization with chemical agents, such as ethylene oxide or gas plasma, does not contribute to the same amount of wear characteristic-improvements as is seen with sterilization by irradiation. Irradiation induces cross-linking of the polymer-chains and this improves the wear properties. Therefore, sterilization with gamma-irradiation is commonly used today. Earlier this was done in an oxygen environment which gave rise to oxidation of the PE due to the free radicals emerging from the irradiation. Oxidation degrades the PE with reduced toughness and reduced crack fatigue resistance as a result (89). To prevent oxidation gamma-irradiation is now performed in an oxygen-free environment of either vacuum, inert nitrogen or argon gas (153). The sterilized product is packed in a vacuum container to prevent oxidation from the free radicals still in the material after the sterilization process. After implantation of the PE component oxygen becomes present again and with that the risk for oxidation. However, the magnitude of oxidation that will occur in vivo is still unclear (154). To neutralize the free radicals emerging from the cascade reaction during sterilization with gamma-irradiation the PE is reheated. This can be achieved in two different ways, either by annealing or remelting the material. Annealing is reheating to a submelting point which will get rid of the free radicals in the superficial layers of the material. Remelting eradicates all the free radicals but it will also reduce the crystallinty in the PE-compound, leading to undesired reduction of mechanical wear properties.

SECOND GENERATION OF HIGHLY CROSS-LINKED POLYETHYLENE

A second generation of highly cross-linked polyethylene (HXLPE) has been developed during the last 5-7 years. The anti-oxidant, α-tocopherol (vitamin E), is used to neutralize the free radicals emerging from the cascade reaction triggered by the cross-linking irradiation of the polyethylene. This makes it possible to fully conserve the improved wear characteristics from cross-linking because annealing or remelting is not longer necessary and at the same time produce an oxidative stability of the HXLPE (90, 100). There are two methods of incorporating vitamin E into the HXLPE. Either vitamin E is blended in the UHMWPE before the consolidation and irradiation processes has started or vitamin E could be diffused into the HXLPE after it has been irradiated. With the latter method a homogenization process is added to obtain adequate amount of vitamin E throughout the material (155). A possible advantage with not having vitamin E blended in the material before the irradiation process could be that the amount of cross-linking of the PE will not be influenced by the presence of an anti-oxidant.

Recently, a new mechanism of oxidation of HXLPE in vitro has been found. Oxygen in synovial lipid fluids has been shown to contribute to PE oxidation even after eradication of free radicals has been done (156). The importance of this mechanism in vivo is not yet known.

Discussion

CREEP AND POLYETHYLENE WEAR

Initially after THA surgery with implantation of a PE-bearing surface the viscous-elastic PE material deforms slowly secondary to load stresses from the articulation. It seems logical to believe that the time perspective for this creep process may vary depending on the properties of the PE. The initial plastic deformation of the PE makes it difficult to evaluate true PE-wear. In the clinical setting, when PE wear measurements are done, a common definition is to count the head penetration rate during the first year as a result of the combined processes creep and true PE wear (92). After the creep process is over, PE wear rate is approximately linear for several years (91).

PE wear could be subdivided into four different types depending on the wear mechanism. Adhesive wear is the wear from two articulating surfaces by pulling away particles from the bearing surfaces. Another type of wear can arise when bearing surfaces articulate against each other in a way not intended, for example a metal head articulating against the acetabular metal shell due to wear-through of the PE-liner. Abrasive wear is when a particle not intended to be there, is causing wear of articulating surfaces. This is also called third-body wear. Common wear particles responsible for this kind of wear are cement particles and HA-particles. The last type of wear is fretting. This is also referred to as backside-wear, i e when the backside of a PE-liner or a PE-insert in a knee prosthesis is rubbing against the underlying metal surface. In THA, running-in is the initial phase of wear when the articulating head finds its place in the PE-liner. Bedding-in is referred to as the setting of the PE-liner in the metal shell. Both this processes increases the conformity and thereby reduces the PE-wear due to lower contact stresses (157, 158).

10.2 DISCUSSION ON METHODS

Surgery

In **studies I-II** the proximally porous and HA-coated stem was impacted to initial press fit fixation, which was often established by three-point contact. In 33 patients in study I and in 13 patients in study II, the gap between the coated stem surface and the surrounding proximal femur was filled with bone chips by impaction from the top. In no case did we fill the femoral canal with retrograde impaction bone grafting before insertion of the stem. Even if the stem is meant for proximal fixation we saw several signs of distal stem osseointegration as well. As is mentioned in "Results" the periprosthetic BMD did not differ between the patients who recieved impaction bone grafting, compared to those who did not. A possible reason for this is the distal ingrowth of the stem leading to load transfer distally, bypassing the proximal bone graft. If the bone graft was not heavily loaded mineralization would not be extensive.

Radiographic methods

Many error sources can deteriorate assessment of subtle skeletal signs on radiographs. Poor quality of the radiographs is a major contributor to this. Position of the patient, especially control of hip rotation, and corresponding projections of the x-ray beams in consecutive examinations cannot be emphasized enough to facilitate assessment of radiographic signs.

The conventional radiographs analyzed in study I and II were mostly radiographic films but the later ones were taken with digitized technique. Digitized radiographs were easier to evaluate because of the possibility to adjust contrast and lightness. These patients had undergone femoral revision surgery, and as a consequence of this, it was sometimes difficult to analyze whether subtle skeletal signs were present or if these were remnants of earlier surgery.

We chose to use two classification systems to determine bone defects prior to revision, the Gustilo-Pasternak (105) and the Endo-Klinik (106) classifications.

The classification from Endo-Klinik is more sensitive to small bone defects (Table 15). Stem subsidence is referred to as a grade II bone deficiency in the Endo-Klinik classification but not in the Gustilo-Pasternak classification. There is also a larger step between a type II and a type III defect in the latter classification.

In **study V** we measured pre- and postoperative femoral offset as the perpendicular distance between center of rotation and longitudinal axis of the femur. Error sources in this evaluation were lack of consistency regarding hip rotation between consecutive examinations but also excessive medialization of the cup could contribute to a functionally decreased offset despite the measured distance being unchanged.

Plain radiography is not a very accurate method in evaluating implant migration or bone remodelling. This is further discussed in the following sections in this chapter.

TABLE 15. ***A schematic division of bone deficiencies in the Gustilo-Pasternak and Endo-Klinik classifications***

Classification of bone defects	Gustilo-Pasternak	Endo-Klinik
I	Minimal endosteal bone defects	Minimal endosteal bone defects Radiolucencies around proximal 50% of the stem
II	Widening of proximal medullary canal Thinning of cortex >50% Defect of endosteal lateral cortex, intact wall Substantial loss of cancellous bone	Stem subsidence Radiolucencies around 100% of the stem Widening of the medullary cavity Moderate loss of cancellous bone
III	Cortical defect in postero-medial wall involving lesser trochanter	Substantial loss of cancellous bone Widening of the medullary cavity including widening of outer femoral diameter Cortical perforation proximally
IV	Loss of cortical circumference below level of lesser trochanter	Extensive or total bone loss of proximal and middle part of femur Substantial loss of cancellous bone and cortical thinning distally

Discussion

EBRA

To improve accuracy in assessment of implant migration on plain radiographs computerized methods, such as Einzel-Bild-Röntgen-Analyse (EBRA), can be used. With manual measurements on plain radiographies a migration of >4 mm can be detected with high accuracy (108), whereas with computerized methods accuracy is improved to 1-1,5 mm (95% CI) (111, 159).

EBRA uses bone landmarks as reference points instead of well defined easily identified Tantalum markers which are used as reference points in radiostereometry. Using bone landmarks will contribute to measurement errors because of bone remodelling or ectopic ossifications, concealing the landmarks between consecutive examinations, but also because of differing projections of x-ray beams between consecutive examinations (160). Compared to radiostereometry more patients are needed to get valid results. The great advantage of computerized methods such as EBRA is that it can be used retrospectively on plain consecutive x-rays, without requiring marking of the implants or the periprosthetic bone.

RSA

Accuracy and precision of RSA has improved with time (161-163). This is a consequence of the more accurate methods used in handling the raw data, such as digitized film cassettes, computerized measurements of marker labeling and edge-detecting techniques to outline the contours of an implant. It is important to have "robust" routines for the Radiostereometric examinations. The most important step to achieve accurate data is the quality of the radiographs. A less than optimal exposure or suboptimal centering of focus can result in too poor accuracy for the examination to be included in the analysis. In **studies IV and V**, 1% and 4% respectively of the RSA examinations were unable to be analyze because of poor accuracy due to technical errors. In these situations last observation was carried forward.

Even though there is an international standardization for analyzing and reporting RSA-results this is not fulfilled perfectly (121). For example, precision could be calculated in different ways and is not always correlated to the study set up from which the results are derived.

A disadvantage with Radiostereometric analyses is the time consuming, and for the manufacturer costly, procedure of marking the implants with Tantalum beads. Development is on-going to circumvent this problem by using applications for marker-free RSA, as in **study V**. By using an edge-detecting algorithm for ellipses the position of a hemispherical shell and a circular prosthesis head can be made without marking of the implants (119).

Other marker-free options for Radiostereometric analyses of hip replacement implants are different model-based methods (164, 165). They base their calculations on CAD-models or on mathematical geometrical reconstructions of the implants. These interesting methods belong to the future in evaluating outcome of hip replacement surgery, but they lie outside the scope of this thesis.

Determining PE wear from plain radiographs can be done with manual methods (166) as well as with computerized methods (167, 168). Accuracy is enhanced even further when radiostereometry is used for PE wear measurements, as in study V (169). In this study Maximum Total Point Motion (mtpm) of the centre of the prosthesis head was used as a proxy variable for polyethylene liner wear. By measuring the vector, mtpm, wear is expressed as a linear process. We know from retrievals of PE bearings at revision surgery, that this is not the case. The prosthesis head wears the PE not in a linear, but in a conical pattern. Thus, wear analysis based on RSA will underestimate the volume of PE particles being abraded from the bearings surface. Development is on-going to validate new RSA techniques for examining volumetric PE wear but, as yet, no such method is in clinical use.

Dual Energy X-ray Absorptiometry (DEXA)

Periprosthetic bone remodelling is a key subject of this thesis. Conventional plain radiography has been shown not to be accurate enough for assessing BMD changes longitudinally. In a study comparing the assessment of BMD changes from plain radiographs, examined by experienced surgeons, compared to true BMD changes, measured with DEXA, it was shown that a reduction of 30% in BMD was necessary before it could be seen as a region with lower attenuation on radiographs (170). A 70% reduction in BMD was needed before radiographic changes in attenuation could be detected with high reproducibil-

Discussion

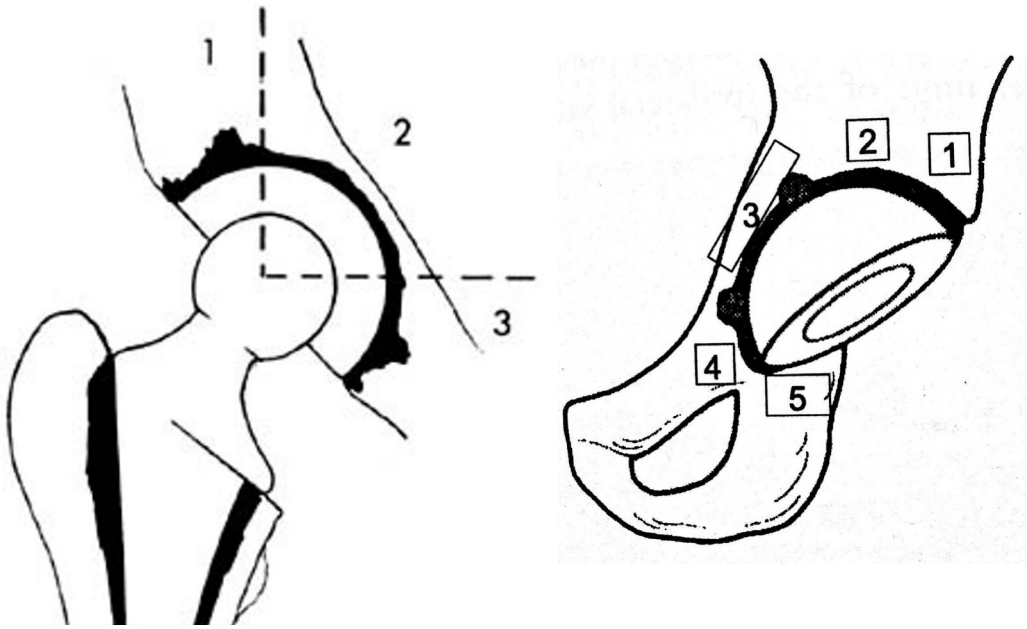


FIG 30. *Schematic drawing of dexa zones according to DeLee-Charnley and Digas.*

ity. In light of this, it is obvious that a more accurate and reliable method than conventional radiography is needed to evaluate periprosthetic BMD changes.

In **study II** the methodology of the BMD measurements was less than optimal. It is convenient to use the contralateral healthy hip as each patient´s own control but there are factors that could distort the comparison. Broaching of the femur during surgery will affect the postoperative BMD. Reduced weight bearing due to pain pre- and postoperatively will also negatively influence BMD measurements in the operated hip. This is not seen to the same extent in the contralateral hip (171, 172). Sometimes this methodological approach is the only one possible, as in retrospective cross-sectional studies. In these situations it is important to measure BMD when bone remodelling has reached a steady state to minimize the effect of the confounders mentioned above.

In longitudinal studies as in studies III-V, it is important to be cautious with the set up, both regarding patient positioning and defining the ROIs, to achieve good accuracy and good reproducibility between consecutive examinations (122, 173).

For conventional stems the Gruen´s zones are well defined and standardized which enables comparisons of BMD analyses from different studies and different stems. For short stems, as in study IV, the current literature is divergent regarding standardization of femoral regions of interests (ROIs). Differences in stem lengths and stem designs influence the positions of the ROIs (35, 174-176). The lack of standardization of ROIs makes it hard to compare bone remodelling results in short stems measured with DEXA .

On the acetabular side ROIs used for BMD analyses are not standardized either. Acetabular zones were originally described by DeLee and Charnley (128) but these were developed for assessment of radiolucencies behind cemented cups (Fig. 30). Digas et al has described another set up of five ROIs for analyzing periacetabular BMD (177). A possible problem with this set up is the risk of measuring varying areas in different patients depending on the anatomy and placement of the cup. It is not simple to define each zone and this might contribute to reduced reproducibility. Wilkinson et al compared the reproducibility of BMD measurements with the three ROI-method described by DeLee and Charnley and the four ROI-method used in study V (126). They concluded that the four-ROI method offered higher precision and,

Discussion

consequently, could differentiate smaller changes in BMD. A disadvantage with the four ROI-method is that it measures BMD changes proximal to the cup as one entity, when there is evidence for differing BMD-changes in the more loaded proximolateral cortical region compared to the more stress shielded proximomedial region (3, 24). To some extent this could be accounted for using the models described by DeLee-Charnley and Digas et al.

Another option is to evaluate BMD with quantitative Computer Tomography (qCT), where the periacetabular bone is scanned at several levels around the cup (178). There are pros and cons with each method. qCT has the ability to distinguish between cortical and cancellous BMD and it is also possible to analyze thin slices of the bone in front of, as well as behind, the shell. On the other hand, precision and accuracy is higher with DEXA which is advantageous when BMD changes over time are subtle (2, 179). The amount of radiation delivered to the patient is much higher with qCT (180).

Clinical outcome measures

An ideal clinical assessment instrument is valid and accurate in its description of a clinical state and it is precise and responsive in demonstrating a quantitative difference in the clinical change measured. The most reliable instruments for measuring clinical outcomes are validated self-administered questionnaires (181), which we have used in all of the studies in this thesis.

Both HHS and WOMAC have a "ceiling effect". It means that the scores are not as sensitive in the high point-range as in the low-point range. In comparative total joint replacement studies the clinical functional improvement is of such a magnitude that it is difficult to find a difference between groups related to implant matters. Even though differences between implants might be of great importance in the long term, the clinical difference related to implant factors, in the short term perspective, tends to be lost in the great improvement normally seen after any type of modern total joint replacement surgery.

Mid-thigh pain is a vague parameter commonly used as an outcome parameter after THA with uncemented stems (16, 43). It is aimed to grade the eventual discomfort or pain from the mid-thigh region derived from excessive load transfer and/or micromotion at the stem tip. Our opinion, after evaluating all the patients in this thesis, is that patients are not perfectly clear over what kind of sensation mid-thigh pain correlates to. As a result of this, pain or discomfort for other reasons, or from other locations than the mid-thigh, was sometimes confounded when patients graded mid-thigh pain. Despite the fact that not many patients in this thesis suffered from mid-thigh pain we think a careful interpretation of this parameter is important.

10.3 INFLUENCE ON BONE REMODELLING BY IMPLANT DESIGN, SURFACE FINISH AND BISPHOSPHONATE TREATMENT

Implant design and surface finish

Attempts to reduce stress shielding-mediated adaptive bone resorption can be done by altering stem design and surface finish of the implants (33, 35, 175, 182). Uncemented stems can be divided into several subgroups based on the design and surface finish. Principally, there are three main categories of stems, cylindrical, anatomical and tapered (183). The evolution of uncemented stems started with extensively coated cylindrical stems aiming for fixation in the femoral isthmus region (184, 185). Due to severe stress shielding of the metaphyseal bone tapered stems were introduced by Zweymuller (186). To further enhance load transfer to the proximal metaphyseal femoral bone, stems were made more bulky proximally (33).

Implant surface finish has also been used to optimize properties for bone ingrowth. By coating the proximal part of a stem with a porous surface layer (39), and sometimes also with HA (147), attempts to mimic physiological loading conditions are stressed even further. However, these theoretical rationales to achieve load transfer proximally have been a disappointment in the clinical setting. Most of the conventional uncemented stems used today do not prevent proximal stress shielding (2, 22, 183).

Isoelastic stems

Apart from altering implant design and surface finish attempts to achieve physiological load transfer has been tried with isoelastic implants, i. e. stems with modulus of elasticity close to bone itself. The first generation of the isoelastic composite stems had poor results because of pronounced osteolysis and aseptic loosening (187). An updated version of an isoelastic stem has shown good short to medium term results regarding bone remodelling and clinical outcome (188, 189). However, 7 years after surgery the bone sparing effect, measured with Dexa, only remained in the calcar region (Gruen zone 7) (190).

An alternative mode of biological fixation was tested in the 1980s. A stem made of cobalt-chromium-molybdenum alloy was coated with a composite material made of polytetraflouroethylene (191-193). The composite surface was reinforced with carbon fiber and designed to enhance fibrous tissue ingrowth. The soft tissue interface was meant to transform load uniformly to the periprosthetic bone, and thus prevent adaptive bone remodelling. The outcome was disappointing with high revision rates due to aseptic loosening and significant BMD loss along the entire stem (194, 195).

Short uncemented stems

Short uncemented stems were introduced in the early 1990s (196), but not until recently has interest for these increased (Fig. 31). The rationales for using short stems is based on the idea of achieving a more physiological load pattern in the proximal femur. Initial implant stability is a key factor for success in biological fixation (65, 68, 112) and the lack of a diaphyseal engaging stem could be a challenge with the use of these components. On the contrary, the absence of a stem is also a key factor in preventing off-loading of the proximal femoral bone. Today, several types of short stems with differing designs are used (Table 16). Generally, in the short term perspective, clinical results have been excellent and stable durable fixation has been achieved (35, 174, 176, 197-201). Disappointingly, the majority of these short stems have not been able to prevent BMD loss in the most proximal femoral regions (197, 198, 202). However, studies on bone remodelling with the Metha stem have implicated load transfer to the proximomedial, i e calcar, region in a study by Lerch et al (203) and in study IV in this thesis we present data that reveals a bone-sparing effect of the ultra-short Proxima stem in the proximolateral, i. e. greater trochanteric, region.

FIG 31.

Periacetabular bone remodelling

Even acetabular implants vary in design and surface finish. The porous titanium construct cup that is examined in **study V** has a trabecular like titanium

Discussion

TABLE 16. ***Studies on bone mineral density (BMD) changes with short uncemented stems in THA. Only studies measuring BMD with DEXA or quantitative Computer Tomography (qCT) are included.***

First author	FU (years)	Hips N	Type of stem	BMD-changes	Comments
Albanese (2009)	3 Cross-sectional	37	Custom made type I vs type II	Reduced BMD loss in ROI 4-5 (5 ROIs)	Stem shortening increased load transfer proximomedially
Kim (2011)	3 RCT	120 (60/60)	Proxima vs Profile (conventional stem)	BMD +9% vs -30% in ROI 1 BMD-10% vs -33% in ROI 7	Short stem reduced bone loss proximally
Logroscino (2011)	1	31 (19/12)	Proxima vs Nanos	Reduced BMD loss in ROI 3-4 (5 ROIs)	Load transfer distally with Nanos stem
Lazarinis (2013)	2 Cohort	30	Collum femoris preserving (CFP)	BMD -17% (zone 2), -28% (zone 6), -19% (zone 7)	Load transfer distally
Schmidt (2011)	3 Cohort	31	CFP	Cancellous BMD -45% Cortical BMD -22%	Metaphysis fixation not achieved but distal fixation
Kress (2012)	7 Cohort	38	CFP	Cancellous BMD -66% Cortical BMD -27%	Metaphysis fixation not achieved but distal fixation
Lerch (2012)	2 RCT	25	Metha vs Bicontact (conventional stem)	BMD -13% zone 1, +13% zone 6, +6% zone 7	Load transfer proximomedially
Chen (2009)	6 Cross-sectional	29	Mayo	BMD -14% zone 1, +9% zone 2, +20% zone 3, -16% zone 6, -18% zone 7	Load transfer distally laterally
Götze (2010)	1 Cohort	36/36	Nanos vs Alloclassic (conventional stem)	BMD -6% (zone 1), +9% (zone 2), -7% (zone 7)	Load transfer distally laterally
Decking (2008)	1 Cohort	20	Cut	BMD +1.4% ROI laterally, -0.4% ROI medially	Small BMD changes. Load transfer laterally.

coating with enhanced porosity aiming for increased bone ingrowth. The porous titanium construct shell is also, at least theoretically, less stiff than a shell with a conventional coating of the same shell size, because the coating is thicker in the porous titanium construct cup. However, despite these two design features, we could not record any bone sparing effect in periacetabular BMD compared to a conventional uncemented cup.

In a study by Field et al the Cambridge cup, with its ultra thin shell, was found to preserve BMD in the zones proximal to the cup (204). This is in contradiction to conventional uncemented shells where BMD in the proximal periacetabular region diminishes after implantation of an uncemented cup, (Table 17) (3, 25, 141, 177, 205, 206). This is explained, at least partly, by the stiff shell giving rise to predominately rim loading, and consequently, proximal and central cancellous bone gets stress shielded. This is more thoroughly discussed in "Discussion on results" in study V.

Bisphosphonate treatment on bone remodelling

During the last decade, several studies have focused on the prophylactic effect of bisphosphonate treatment on bone remodelling adjacent to orthopedic implants. The aim is to prevent periprosthetic bone loss and to enhance the mechanical stability of the components. Both these parameters are associated to the long-term outcome in THA (40, 114, 115). Generally, there is a bone sparing effect during on-going treatment with bisphosphonates but the effect seems to be transient, with diminishing BMD after cessation of the drug. However, the pattern of periprosthetic long term changes in bone mineral after treatment with bisphosphonates is not unanimous (53). Wilkinson et al noted less bone loss in the femoral calcar region 2 years after THA followed by 6 months treatment with pamidronate (207). Arabmotlagh et al compared BMD changes in THA patients receiving either alendronate or placebo postoperatively. BMD remained higher in the treatment group, compared to the placebo group, 1 year as well as 6 years after surgery (32). Single dose treatment with pamidronate was followed by higher BMD 6 months after surgery in a randomized controlled study by Wilkinson et al (208) but no difference in BMD was seen after 5 years (209). The long term effect of infusion of Zoledronic acid 2 weeks and 12 months after surgery, compared to placebo, revealed less femoral BMD loss in the treatment group up to 2 years after surgery (210). The differences in the effects recorded could depend on different properties of bisphosphnates.

Bisphosphonates have also been shown to reduce implant migration of uncemented acetabular components in THA and cemented tibial knee components in total knee arthroplasty (TKA) (54, 55). In animal

Discussion

models, locally eluted zoledronic acid from the HA-coating in porous structured implants improved the mechanical stability of the implant and enhanced the amount of bone ingrowth (211, 212).

Thillemann et al. conducted a nationwide population-based study on the use of bisphosphonates and risk of revision after THA in osteoporotic patients (213). No decreased risk ratio was found for aseptic loosening between users and non-users. However, a subgroup analysis revealed lower risk for revision in patients who had had bisphosphonate therapy for more than 8 months. This finding together with what we (in study III) and others have found regarding increased bone loss in patients with low preoperative BMD may warrant prolonged treatment with bisphosphonates after THA in osteoporotic patients. However, evidence for the risk of atypical insufficiency fractures in the subtrochanteric region after prolonged treatment with bisphophonates is still debated (214-216). A risk-benefit perspective must always be considered before prolonged treatment with bisphosphonates is initiated.

It is important to mention that despite what has been discussed above about the efforts to prevent periprosthetic bone loss, the mechanically induced adaptive bone resorption as a mechanism for prosthetic loosening is controversial (43, 188). Increased incidence of femoral osteolysis or implant loosening has not been directly associated with stress shielding (44). It is also unclear whether varying degree of stress shielding, seen with different implant designs, will have a clinically significant effect on the reduction of other, late coming, complications such as periprosthetic fractures.

TABLE 17. ***The effect on bone remodelling of different cup designs in THA. Only studies using DEXA or quantitative computed tomography (qCT) are included. Bearing surfaces in the articulations were metal heads on polyetheylene in the studies by Laursen, Baad-Hansen, Digas, Lazarinis and Field. In studies by Penny, Kim and Schmidt bearing surfaces were ceramic heads on polyetheylene. Lazarinis et al from 2013 are unpublished data from his thesis.***

First author	FU (years)	Hips N	Type of stem	BMD-changes for Titanium cups	Comments
Laursen (2007)	3 RCT 2 grp	89	Titanium shell with titanium fiber-mesh ± HA	Wilkinson´s 4-ROI	BMD reduction in zone 1-3. BMD gain in zone 4. No difference between coatings.
Baad-Hansen (2011)	2 RCT 2 grp	50	Titanium shell with trabecular tantalum vs titanium fiber-mesh coatings	Wilkinson´s 4-ROI	BMD reduction in all zones. Most pronounced in the two proximal. No difference between cup designs.
Penny (2012)	2 RCT 2 grp	39	Titanium shell vs CoCr resurfacing shell (ASR)	Wilkinson´s 4-ROI Zone **1** -5% **2** -9% **3** -0.6% **4** +4%	BMD reduction in zone 1-3. BMD gain in zone 4. No difference between cup designs
Digas (2006)	2 RCT 3 grp	88	Titanium shell PC/ HA Cemented all poly cup with Flouride cem Cemented all poly cup with gentamicin	5-ROI metod. Zone **1** -3% **2** -6% **3** -17% **4** +4% **5** +8%	BMD reduction proximally and medially. Uncemented cup looses more bone. No differences between cemented cups.
Lazarinis (2013)	2 Cohort	29	Titanium shell with porous- and HA coating. Equatorial threads	5-ROI metod. Zone **1** -13% **2** -16% **3** -10% **4** +13% **5** -0.8%	BMD reduction proximally and medially. BMD gain distal medially
Kim (2007)	5	100 (bilat THA)	Titanium shell with porous coating and alumina vs polyethylene bearing	DeLee-Charnley´s 3-ROI Zone **1** 20% **2** -25% **3** 1%	BMD reduction proximal medially. BMD gain proximal laterally
Field (2006)	2 Cohort	11	Horseshoe shaped extremely thin carbon inforced polymer shell ± HA	DeLee-Charnley´s 3-ROI Zone **1** ~±0% **1-3** -6% **2** ~±0% **3** ~-14%	All patients were female with neck of femur fractures. BMD returned to baseline proximally.
Schmidt (2012)	7	38	Titanium shell with porous- and HA coating. Equatorial threads	BMD Cancellous / Cortical cranial -30% / 5% ventral -62% / 22% dorsal -84% / 19%	BMD measured with Quantitative Computed Tomography.

Discussion

10.4 DISCUSSION ON RESULTS

Study I

The aim of using proximally coated stems in femoral revision surgery is to enhance proximal fixation and thereby minimize load transfer distally. The key parameter to achieve good results with these stems is the degree of bone loss at revision (18, 19). Extensive bone loss will prevent initial rigid, press fit fixation of a conventional proximally coated stem. Continuous micromotion in the interface between stem surface and host bone can result in fibrous fixation (68, 217), or absence of fixation which, of course, will give poorer clinical outcome. The clinical outcome from studies using proximally coated stems in uncemented femoral revisions are listed in (Table 18).

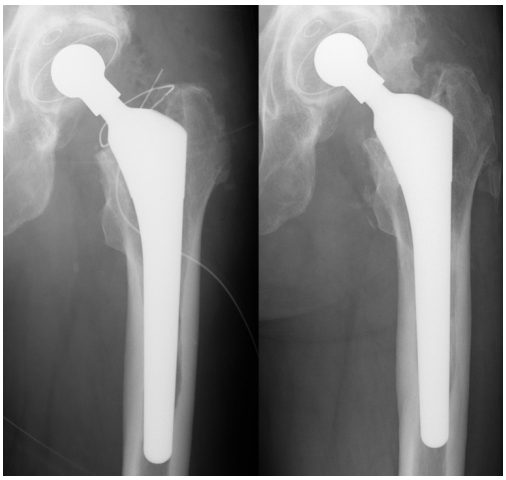


FIG 32. *The linear osteolysis along the stem postoperatively has been filled out with new bone formation*

CLINICAL RESULTS

A mean HHS of 75 at follow-up, (range 30-100) is slightly lower than what others have reported (18, 19, 218). This might be a consequence of the large proportion of patients in Charnley class C in this study. We presented the clinical outcome in HHS subdivided in category groups (excellent, good, fair and poor). We have learnt that this is not recommended because score data is on the ordinal level because the scale is not continuous and proportional. A score parameter given a value of 8 instead of 11 does not reflect a statistically significant difference in function between two patients but it could lead to the patients being assigned to different outcome categories. This will distort the interpretation of the clinical outcome (219).

RADIOGRAHICAL RESULTS

We chose to use two classification systems to determine bone defects prior to revision, the Gustilo-Pasternak (105) and the Endo-Klinik (106) classifications.

As a consequence of the relatively small bone defects at revision we were able to achieve initial sta-

TABLE 18. ***Studies on outcome after femoral revision with proximally coated uncemented stems.***

First author	FU (years)	Hips N	Type of stem	Survival rate	Comments
Berry (1995)	8	375	6 different types	58 % aseptic survival rate	Insufficient fixation proximally due to inadequate bone stock
Woolson (1995)	6 (4-8)	28	Straight, cylindrical	80 % survival rate	Bone defects moderate to severe. 52% radiographically unstable
Peters (1995)	5 (4-7)	49	Long, curved	96% for revision , 37% for revision or subsidence	High incidence of progressive subsidence
Malkani (1996)	3 (2-5)	69	Metaphyseal filling, long, curved	82 % for entire group. 58 % for fracture group	Perperative fracture in 46 %
Mulliken (1996)	5 (4-6)	52	Metaphyseal filling, long, curved	76 % overall mechanical survival rate	Peroperative fracture in 40 %. Insufficient fixation if moderate or severe bone defects
Suominen (1996)	5	39	Long, curved	72 % overall mechanical survival rate	High incidence of revision or radiographical loosening
Emerson (2003)	12 (9-15)	66	Metaphyseal filling, long, curved	94 % overall and 97 % aseptic survival rate	Used strut allografts if insufficient bone stock proximally
Kelly (2006)	5 (4-7)	33	Straight, tapered	100%	Good results if sufficient bone stock.
Salemyr (2006) Study I	6	62	Straight, tapered	95 % overall survival rate	Bone defects mild to moderate
Khanuja (2013)	4	19	Straight, tapered	95% aseptic survival rate	Bone defects Paprosky type I-II.

Discussion

bility of almost all implants (Table 19). Nineteen of the stems initially subsided a few millimeters in the sclerotic tubular proximal femur but the imprecise method for analyzing migration in this study, plain radiography, could not establish this with certainty in more than five stems (108), that had subsided 5-8 mm. However, at follow-up all stems showed evidence of being well fixed but the aim to achieve predominately proximal load transfer was not fulfilled. Periprosthetic bone remodelling revealed several signs of stress shielding.

Periprosthetic linear osteolysis, seen in almost everyone of the patients at revision, had diminished substantially at follow-up, (Fig. 32). The reason for this was the rigid fixation of the stems, enabling load transfer to the surrounding bone and subsequently a drive for bone remodelling according to Wolff´s law (21).

COMPLICATIONS

Nine patients suffered from dislocation. This high dislocation rate is most likely the result of a combination of several factors; the use of small head sizes (22, 28, 29 mm), a posterolateral surgical approach without repair of the posterior capsule and that only one offset version of the stem was available during the first years of surgery.

TABLE 19. ***Bone defects were predominately type II in both classifications, and no type IV defect was observed. Femoral bone defects at revision (53 hips)***

Type	Gustilo and Pasternak	Endo-Klinik
I	17	4
II	35	38
III	1	11
IV	0	0

Study II

CLINICAL AND RADIOGRAPHICAL OUTCOME

The clinical and radiograhical results in study II were similar to study I, since the study cohort derived from the patients included in study I.

PERIPROSTHETIC BONE MINERAL CHANGES

Because of the retrospective design of this study we used the contralateral healthy hip as control to evaluate femoral periprosthetic BMD changes after aseptic uncemented stem revision. The inherent methodological problems that arise with such a study design are discussed in "Discussion on methods".

We analyzed whether differences in time elapsed from surgery to follow-up had any influence on reduction of BMD. We found no such correllation and the R^2-coefficient was 0,021 for the entire periprosthetic region as an entity (Gruen zones 1-7) and 0,016 for the proximal four zones (Gruen zones 1-2 + 6-7). This is probably an effect of that we did the measurements more than 2 years after surgery, when the initial postoperative bone remodelling process had reached a steady state (129).

The radiographic results, as well as the BMD changes, revealed that the proximally coated stem became osseointegrated both proximally and distally. The large reduction in BMD was most pronounced in the four proximal Gruen zones (1-2 and 6-7), indicating that the stem design could not prevent load transfer distally.

In **study II** both the amount and the extent of BMD loss was larger than after primary THA with the same stem (2, 142). Patients who require stem revision have femoral bone stock of lower quality, and with lower BMD, than patients undergoing primary hip arthroplasty. Because of lower preoperative BMD, and the need for larger diameter stems to achieve initial stability, stress shielding after femoral revision will be more pronounced than after primary hip arthroplasty (33, 142).

BMD reduction did not differ between patients who had been bone grafted proximally from those who had not. The reason for this is probably the inherent rigidity of the stem which, to some extent, by-passed the bone grafted regions. Consequently, mineralization of the newly formed bone in the grafted region was not extensive. However, it cannot be ruled out that bone grafting had some influence, since the measured BMD-loss is larger in zones 2 and 6 compared to zones 1 and 7.

In 19 of 21 patients the linear periprosthetic osteolysis present at the time of revision was filled out with new bone formation. Despite this new bone formation BMD was markedly reduced, probably due to load transfer distally, as is mentioned above.

Discussion

Study III

During the last decade, several studies on periprosthetic bone remodelling after THA have shown the possibility of reducing periprosthetic bone resorption with bisphosphonate treatment (31, 32, 52, 207, 208). In study III we evaluated whether risedronate, taken once weekly for six months after uncemented THA, influenced periprosthetic femoral BMD changes up to 2 years after surgery.

RADIOGRAPHICAL CONSIDERATIONS

When we analyzed the conventional radiographs we saw several signs of distal load transfer, such as calcar atrophy, distal cortical hypertrophy, pedestal formation at the stem tip and, in severe cases, diminishing attenuation of the proximal bone. We could correlate loss in BMD, measured with DEXA, to radiographical signs of disuse atrophy proximally but gain in BMD could not be correlated to signs of load transfer distally. This could be interpreted as indirect evidence of the low sensitivity for evaluating bone mineral remodelling with conventional x-rays (170).

We found significantly less endosteal bone bridges, i e spot welds, in the risedronate group even though all stems, in both groups, showed evidence of being well fixed. A probable explanation for this is the inhibition of osteoclasts by risedronate, leading to altered and diminished bone remodelling. Reduced bone metabolism may not be entirely positive and whether reduced bone turnover will result in a more brittle skeleton and an increased risk of atypical fractures is unclear (214-216).

PERIPROSTHETIC BONE MINERAL CHANGES

After THA, bone remodelling is most pronounced during the first months (129). In study III we chose to intervene with risedronate for six months. Our hypothesis was that by inhibiting bone resorption during the period when bone remodelling is most intense, the overall bone loss should be minimized. However, expectations of that the phase with steady state low continuous bone metabolism should be entered in the same manner, and in the same time span, as in the natural situation was not fulfilled. Our results revealed that the initial intense bone resorption was only postponed until the bisphosphonate treatment was ended. After cessation, a more rapid bone loss was recorded in the treatment group, especially from 12 to 24 months, in comparison to the placebo group. This phenomenon is clearly visualized in (Fig. 23) as a steeper slope of the curves in the treatment group, between 12 and 24 months.

We calculated the median BMD in general bone mass preoperatively and from that dichotomized the patients in two groups, one with low and one with high general bone mass. Patients in the placebo group with low pre-operative bone mass had lost 23% and 27% in zones 1 and 7 of the operated hip after 2 years, whereas patients with high systemic BMD lost only 14% and 11% respectively. This is consistent with results from earlier studies showing a correlation between low preoperative bone mass and increased bone loss around uncemented stems (33, 220). Another factor influencing periprosthetic BMD was the stem diameter. Stems were divided in three groups with differing stem sizes. Larger sizes were associated with increased bone resorption in zone 1 (p=0,045). This is in accordance with earlier reported results as well (142).

According to the "intention to treat"-principle used in this study, 3 patients in the risedronate group were included in bone remodelling analyses despite discontinuation of the active substance. This reflects the clinical situation where patients will stop their medication if side effects arise. If these patients are excluded from the analyses the effect of the studied drug will be boosted compared to a clinical setting.

Study IV

Interest for short stems in THA is increasing. The rationale for this is the desire to be as conservative as possible because of the assumption that people will live with their hip replacement for longer periods of time in the future.

Not all short stems fulfill the aim of saving bone in the most proximal femoral regions (Table 16). However, shorter stem lengths will inevitably leave more of the proximal femoral diaphysis untouched and, consequently, preservation of femoral bone stock is favored by the use of shorter stems.

PERIPROSTHETIC BONE MINERAL CHANGES

BMD loss in the periprosthetic region as an entity, ie Gruen zones 1-7, was -0.3% (SD±7.8) for the ultra-short stems and -5.5% (SD±4.7) for the conventional stems 2 years after surgery (p=0.008). The BMD result for the ultra-short stem compares favorably with other short stems with equally excellent clinical outcome reported. Bone loss around the Metha stem was found to be -2.8% two years after surgery (203) and -3.3% six years after implantation of the Mayo stem (197). Whether a 5% reduction in BMD in the short-term perspective is sufficient to reduce the incidence of periprosthetic fractures is still unknown, but a BMD reduction of the same magnitude has been found to reduce the relative risk of hip fractures in an elderly osteoporotic clientele (49).

IMPLANT MIGRATION

Bone quality is a key parameter to achieve rigid press fit fixation with a metaphyseal stem (99, 221, 222). We found that the short stem used in study IV was not as forgiving as a conventional stem regarding surgical technique and that correct implant sizing is mandatory to achieve good fixation. The initial varus migration was larger in the ultra short stem group than in the conventional stem group (Fig. 33). After 2 years the ultra-short stems had migrated 1.71 mm (median, range 0.39-6.00), which was 0.84 mm more than the conventional stems (p=0.014). This is a slightly larger migration than the proposed safe zone for an implant not having an increased risk of later loosening (114). However, no migration occurred after the three months follow-up and therefore it seems reasonable to assume that long-term fixation of the implants is not at risk (115, 223).

CLINICAL OUTCOME

We found a trend for larger improvements in clinical scores with the ultra-short stem. The power analysis was not based on the clinical outcome and the difference might have been statistically significant if a larger number of patients had been included. On the other hand, hip specific clinical outcome scores do not have high responsiveness measuring outcome in the upper range of the scale. Consequently, a clinically important difference between two implants may be lost in the great improvement normally seen after any kind of modern joint replacement surgery.

It is important to emphasize that the excellent outcome in this study relates to patients with good bone quality. We do not know whether we would obtain similar results in patients with compromised bone stock, even though others have used the ultra short stem in elderly patients and reported good results (224, 225). In our opinion, patient selection and surgical technique are crucial factors for a successful outcome. Preceding this randomized study we conducted a pilot series of 19 THAs with the ultra-short stem. In the pilot series we had two cases with aseptic loosening of the stem due to insufficient primary stability. It is probable that the pilot series contributed to the low complication rate and excellent results reported in study IV.

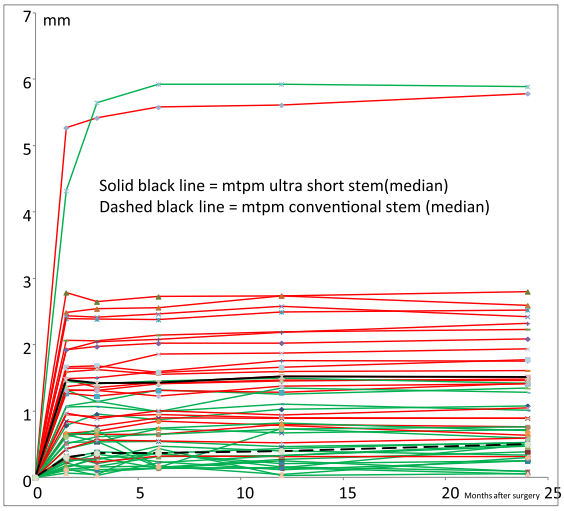


FIG 33. *Varus migration in millimeter for individual stems. Red lines for ultra-short stems, green lines for conventional stems.*

Discussion

Study V

Problems related to the acetabular component are the most frequent mode of failure in contemporary uncemented THA (10, 11). Periacetabular bone loss derives from wear debris-induced osteolysis and from stress shielding-mediated BMD changes behind stiff metal shells (11, 24). To improve the long term outcome, it is important to develop better materials to reduce the production of wear particles and to enhance bone ingrowth into the porous surface of the backside of acetabular shells.

In study V we have focused on these two questions.

PERIPROSTHETIC BONE MINERAL CHANGES

In study V there was a trend towards less bone loss in the zones behind the porous titanium construct shell, i e Wilkinson´s zones 2 and 3, compared to corresponding zones for the conventional shell. The difference did not reach statistical significance, probably due to larger standard deviations for the BMD-measurements in the porous titanium construct cup. It is possible that bone ingrowth was more pronounced in the coating with increased porosity (62, 63). Another possible explanation that might contribute to the trend for higher BMD in the zones behind the porous titanium construct cup could be the thickness of the coatings. This is 1.5 mm in the porous titanium construct cup and much less in the conventional cup, where it consists of three layers of titanium sintered beads. For a certain size of cup the solid titanium shell underlying the coatings is therefore thicker in the conventional cup. This will lead to different modulus of elasticity and as a consequence of that the adaptive bone remodelling might differ.

There is a lack of standardization of how to measure periacetabular BMD changes after THA. Different regions of interest are used but also different measuring methods. A draw back with the most common method, DEXA, is its inability to differentiate between BMD changes in cancellous bone from that in cortical bone. A reduction of BMD in Wilkinson zone 1, proximal to the cup, could be an effect of pronounced bone loss in cancellous bone and at the same time gain, or at least stable, BMD in the cortical bone. Finite element analysis (FEA) (226) and BMD measurements with quantitative computer tomography (qCT) (3, 24, 178, 227, 228) reveals such a pattern of BMD changes, i. e. rim loading of cortical bone and shielding of central cancellous bone.

In general terms, in opposition to what was thought to be the case according to FEA-analysis and Wolff´s law, the load pattern after press fit fixation of uncemented acetabular implants induces a reduction of BMD in the proximal and medial regions, and stable or increasing BMD in the distal regions (25, 141, 177, 205). The results listed in (Table 17) are from titanium acetabular shells. Despite differences regarding the type of material and finish of the coatings, the pattern of bone remodelling was similar.

The reasons for increasing BMD in the distal regions are not clearly understood. A contributing factor could be that, by reaming during surgery, the shells are medialized to the absolute proximity of the distal medial acetabular wall. This region is normally covered by the central ligament of the femoral head and perhaps, forces will be transmitted from the backside shell to the underlying bone, to a larger extent than in a native hip joint. This possible explanation is in accordance with the results of the Cambridge cup published by Field et al (204). This extremely thin, metalbacked polyethylene cup has the shape of a horseshoe, and thus does not transfer load to the distal medial region of the acetabulum. BMD in zone III according to DeLee-Charnley classification was reduced in this study, contrary to what is seen with hemispherical acetabular implants. In the same study, no reduction in BMD was recorded in the proximal regions, ROI I and II. This is also in opposition to other studies. A possible reason could be the difference in metal shell thickness. In the Cambridge cup the shell is only 1.5 mm thick, compared to a standard shell where the thickness of the solid titanium is approximately 3.5-5 mm. The difference in modulus of elasticity will give rise to different load patterns transferred to the underlying bone.

IMPLANT FIXATION

Implant fixation was excellent with both types of shell. During the first six months migration occurred, predominately, as rotation around x- and y-axes. Even though the amount of migration was above the level, suggested by Pijls (117) to be "ac-

ceptable", we think that fixation of the cups is not "at risk" of inferior results due to loosening, because no continuous migration was seen. It is possible that the larger initial migration seen in the porous titanium construct cup is an effect of its higher friction coefficient. As a result of this we may not have been able to impact the shell during surgery all the way in to the acetabular bone, as often as we were able to do with the conventional shell.

POLYETHYLENE WEAR

How long the creep process, i e deformation of the polyethylene without production of wear particles, will continue after THA is not well defined. It may vary depending on different manufacturing processes of the polyethylene, for example, the amount of cross-linking radiation. In some studies the creep process is assumed to continue for approximately 2 months (93), and in other studies for up to 12 months (92) after surgery.

In study V we decided to present head penetration data up to 12 months, as a result of the combined processes polyethylene creep and wear. Steady state-head penetration is recorded between 12 and 24 months for the conventional liner but not for the α-tocopherol-treated liner. Whether this is a coincidence, or a matter of extended time for the creep process in this type of polyethylene, is unknown. Undoubtedly, the α-tocopherol-treated polyethylene was harder, resulting in less head penetration during the first postoperative year. Bearing in mind the short time perspective, two years in this study, and the uncertain factor of how long creep should be considered as a parameter influencing head penetration data, calculation of true polyethylene wear is not reliable in our study.

A big difference between the groups in postoperative offset might had influenced the results of polyethylene wear. We recorded a 3.7%, equal to 1.5 mm, larger increase in postoperative offset in the conventional cup group. Some studies have shown that an offset polyethylene liner wears more than a conventional liner (229, 230). On the contrary, in a study by Sakalkale et al, it was found that lower offset, and inability to restore preoperative offset, resulted in higher polyethylene wear (230). We do not consider the small difference in restoring offset, between the two groups, had any impact on the PE wear outcome in this study. ⊙

Discussion

10.5 STRENGTHS AND LIMITATIONS

Study I

The retrospective study design is a weakness in study I. It would have been preferable to have recordings of HHS prior to revision.

Conventional radiographs on plain films was not an optimal method for detailed analysis of dynamics of osteolysis, or other subtle skeletal signs of bone remodelling. It was sometimes hard to differentiate between, for example, disuse osteopenia and focal osteolysis, or to identify spot welds or reactive lines. In some radiographs there were non-specific skeletal signs left as remnants after earlier surgery which also contributed to difficulties in the radiographical analysis.

The strengths of this study were the relatively large sample size and that we were able to re-examine all patients who were still alive.

Study II

Apart from what is mentioned for study I regarding the retrospective study design, the lack of baseline measurements of periprosthetic BMD and general bone mass were limitations in study II. The use of the contralateral hip as the control for periprosthetic BMD changes is suboptimal. There might have been a side difference in BMD preoperatively and broaching during surgery could also have influenced BMD. If the contralateral hip is to be used for comparison, results will be more accurate if measurements are done when bone remodelling is stationary, i. e. more than a year after surgery, as in study II (140).

Study III

The use of EBRA instead of RSA gave lower resolution in the implant migration analysis. Two different concepts of cup fixation, cemented and non-cemented, were used. However, the type of PE used in both cup types was the same. It is known from a previous study that difference in bearing materials did not affect BMD in the proximal femur in the short term perspective (231).

The strengths in study III were the randomized double-blinded study design, the high follow-up rate and large sample size, and that the outcome analysis was done according to intention-to-treat-principle.

Study IV

Originally, when we planned this study, we intended to analyze implant migration in six degrees of freedom with radiostereometric analysis. The uneven distribution in the two groups of Tantalum-marked stems made this impossible.

From a methodological point of view, the trial would have benefited from a blinded study design but we do not believe that not having such a design influenced the outcome.

The strengths of this trial were the prospective randomized protocol, the high follow-up rate, an adequate sample size as determined on the basis of a power analysis and that we evaluated our primary and secondary endpoints with highly accurate examination methods.

Study V

The study was not blinded but the analysis of efficacy was performed according to the intention-to-treat principle. A weakness in the study design was the difference in liner design and the amount of irradiation used to crosslink the polyethylene.

The strengths were that we were able to follow all the patients, with none were lost to follow up, and the highly accurate methods used to evaluate bone mineral density, implant migration and polyethylene wear ⊙

10.6 GENERAL DISCUSSION

Aspects on change in indications for THA

As a consequence of the excellent clinical outcome after THA, the indications for hip-joint replacement surgery have widened. A potential problem is that the results achieved in the slightly older population undergoing surgery today may not apply when younger and more active patients undergo THA surgery. We know from hip arthroplasty registers that the outcome in the younger group is not as good as those of the older group (1) (Table 20 & 21). People living in developed countries tend to be older, healthier and have a more active life style. This will contribute to higher demands on hip replacements being carried out today. The implants will have to endure forces of greater magnitude over longer periods of time than those which are showing excellent results in the hip arthroplasty registers of today. This is a reality that will have to be considered as we continually strive toward excellent long-term outcome. More long-lasting implants that have the advantage of conserving the biological environment in the hip, facilitating subsequent re-operations, should the need arise, is the target goal.

Influence on bone remodelling by implant design, surface finish and bisphosphonates

One way to conserve the local biological environment is to influence adaptive bone remodelling, to reduce periprosthetic bone loss. The studies in this thesis focus on illuminating the options to do so by altered implant design, implant surface finish and pharmacologically with the use of bisphosphonates. Implant mediated bone loss through stress shielding can be influenced by stem design, at least in the short term perspective (33, 35, 182, 232).

Bisphosphonates influence two proxy-variables for long term outcome in THA, i e. periprosthetic bone loss and implant migration. Stress shielding-mediated bone loss can be reduced with bisphosphonates (30, 32, 207) but today it is not known how long the treatment should be continued. There are some well known negative side effects of this pharmacological treatment, but in the future, as it is expected that patients will live longer with their prostheses,

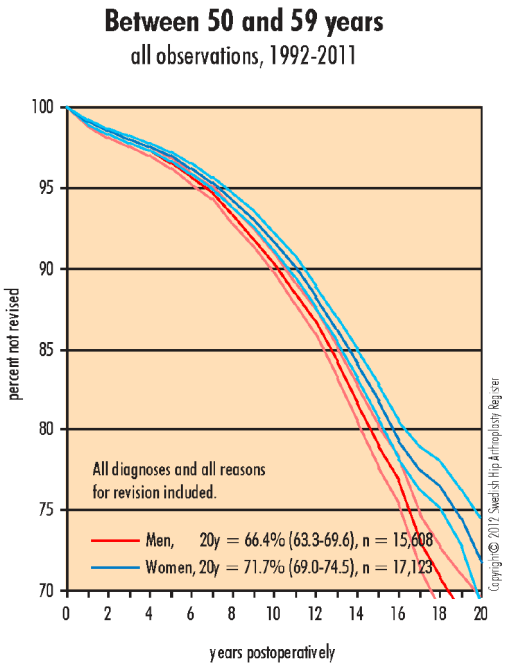


TABLE 20. *Reprinted with permission from the Swedish Hip Arthroplasty Register (SHAR).*

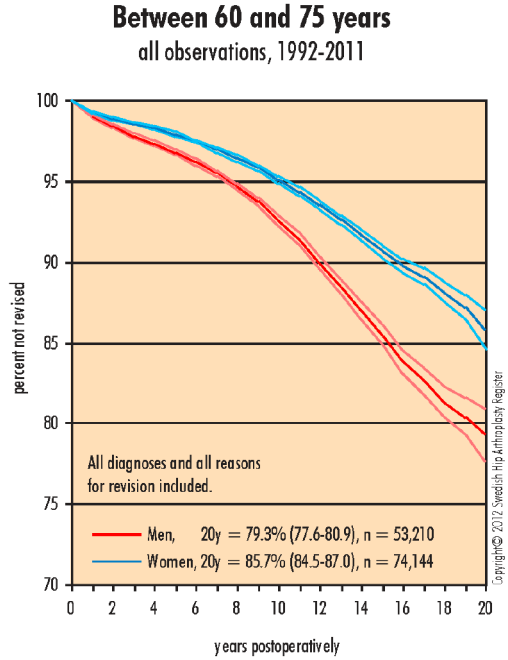


TABLE 21. *Reprinted with permission from the Swedish Hip Arthroplasty Register (SHAR).*

Discussion

one can question whether this is the best treatment in order to reduce periprosthetic bone resorption (214, 215). It might have a place in improving the clinical outcome in certain categories of patients, for example, those with severe osteoporosis or patients undergoing hip revision where bone stock is severely compromised.

Altering implant surface finish with bioactive coatings, such as HA, has not been shown to reduce periprosthetic bone resorption. However, in recent register studies the same type of coating resulted in a higher incidence of cup and liner revisions in primary and revision settings (78, 152). One probable explanation is that the release of HA-particles leads to third-body wear. HA-coating does not improve long term outcome in a well functioning uncemented tapered stem (77). From these results, and from what we know about the properties of HA in this thesis, it appears as though HA coating has a positive effect primarily on early implant fixation and may prove to be a drawback for the long-term outcome.

Altering implant surface finish with a type of bio-friendly metal (Tantalum) or a new geometrical titanium-coating architecture has been shown to increase bone ingrowth in laboratory tests (37, 62, 63). In a clinical setting, less bone resorption could not be shown with tantalum coating (141) and we could not verify this either in study V. Even if these new implant surfaces with enhanced porosity may not have a bone sparing effect, the higher friction coefficient makes them suitable in cup revision surgery where they expand the arsenal of implants to give good primary fixation in compromised host bone.

Clinical relevance of stress shielding

As yet, no studies have shown a correlation between periprosthetic BMD decrease and revision rate or clinical outcome. However, in total hip replacement, periprosthetic fractures are an increasing problem as the population ages and have an increased risk of falling. Continuous on-going bone loss ought to be disadvantageous for the long term outcome in these patients. Furthermore, stress-shielding could increase the risk of periprosthetic fractures and implant loosening. The drawbacks may not be apparent until sufficient "exposure time" has elapsed. From studies done on the reduced risk of osteoporosis-related hip fractures with prophylactic treatment using bisphosphonates, it seems reasonable to suppose that the same relationship could be true in THA (49). This suggests that a reduction in BMD loss of approximately 5-10% could reduce the incidence of late onset periprosthetic fractures.

Clinical relevance of osteolysis

There is an on-going debate as to whether stress shielding predisposes to osteolysis, but it has not been verified in clinical studies (43, 44). However, an association between polyethylene wear and osteolysis has been shown (47), both on the pelvic side (11, 45) and on the femoral side (42). In these studies it was evident that periprosthetic osteolysis was a risk factor for implant loosening and poor clinical outcome in THA. A possible consequence of this association is that outcome can be improved by reducing polyethylene wear. Highly cross-linked polyethylene (HXLPE) liners, with improved wear characteristics, are an attempt to reduce periprosthetic osteolysis and achieve better clinical outcome. This should hold true unless the wear particles released from HXLPE liners, though fewer in numbers and smaller in size, induce a more aggressive osteolytic reaction compared to conventional PE wear particles (233, 234).

A second generation of HXLPE liners is now being used in THA. To get rid of the oxidation-prone free radicals emerging from the cross-linking irradiation, the antioxidant vitamin E has been used in the manufacturing process. Wear characteristics for the vitamin E-treated HXLPE has been promising in laboratory tests (100), but no long-term results from a clinical setting are yet available. In the short two year perspective, as in study V, no conclusions of PE wear rate can be drawn. Whether these new bearings will reduce PE wear, and consequently reduce the periprosthetic osteolysis, on-going randomized controlled trials, as study V, will tell.

11 CONCLUSIONS

I Aseptic femoral revision with a proximally porous- and hydroxyapatite-coated tapered stem is a reliable procedure, with encouraging results, in the mid-term perspective, if bone defects at revision are moderate

II Aseptic femoral revision with a proximally porous- and HA-coated tapered stem gives good clinical results but pronounced proximal femoral bone demineralization.

III Risedronate given once weekly for 6 months after THA is effective in preventing periprosthetic proximal bone loss after THA around an uncemented stem up to 12 months, with a trend towards an effect up to 24 months postoperatively.

IV An ultra-short uncemented anatomical stem gives less periprosthetic bone loss and equally excellent stem fixation and clinical outcome, compared to a conventional tapered stem, up to 2 years after THA.

V Comparing two acetabular titanium implants with different properties regarding shell backside surface coating and articulating polyethylene showed no differences in periprosthetic bone loss, cup migration or polyethylene liner wear, up to 2 years after THA.

GENERAL CONCLUSION

In summary, adaptive periprosthetic bone remodelling after primary uncemented total hip arthroplasty could be reduced pharmacologically with bisphosphonates and with altered stem design. Periacetabular bone demineralization could not be reduced with a new porous titanium construct material. Alpha-tocopherol diffusion of HXLPE liners gave reduced creep, but not less polyethylene wear up to 2 years after surgery.

Periprosthetic bone resorption 6 years after aseptic femoral revision was profound.

12 IMPLICATIONS FOR FUTURE RESEARCH

Future research in hip arthroplasty surgery should focus on

* the association between polyethylene wear, occurrence of periprosthetic osteolysis and when to interfere to prevent implant failure

* the options to interfere with clinically relevant adaptive bone resorption, to reduce the incidence of late occuring periprosthetic fractures

* which patients who should benefit from bisphosphonate treatment after THA and for how long such treatment should go on.

* the possibilities to interfere with periprosthetic bone metabolism through the RANK- RANKL-osteoprotegerin (OPG) system.

13 SUMMARY IN SWEDISH – SAMMANFATTNING PÅ SVENSKA

Höftproteskirurgi är en framgångsrik behandlingsmetod både för patienten och för samhället. För patienten beror det goda resultatet på den effektiva smärtlindrande effekten som operationen medför och för samhället innebär detta att arbetsföra personer klarar sin försörjning och potentiellt hjälpbehövande äldre personer klarar ett självständigt liv, i större utsträckning efter operationen än före.

Frekvensen av höftprotesoperationer har varit stigande under en lång rad av år och i Sverige idag utförs drygt 16 000 höftprotesoperationer årligen. De goda långtidsresultaten har bidragit till att yngre och aktivare människor, med smärtproblematik från höftlederna, nu blir opererade i högre omfattning än för ett decennium sedan. Det är dock väl känt att långtidsresultatet vid höftproteskirurgi inte är lika bra hos yngre människor som hos äldre. Inte heller vet man idag hur riskbilden att leva med en höftprotes i 20-30 år, eller ännu längre, kommer att se ut. Samtidigt som allt yngre människor opereras förväntas medellivslängden fortsätta att öka. Sammantaget kommer detta att leda till att andelen människor som lever med en höftprotes i flera decennier ökar markant i framtiden. Det är därför viktigt att kartlägga vilka risker detta medför samt hur riskerna kan motverkas.

Fixation av proteskomponenter sker antingen med hjälp av bencement eller på biologisk väg, genom att skelettet ”växer in” i den mikroporösa titanytan som täcker proteskomponenter ämnade för biologisk fixation. Denna avhandling fokuserar enbart på komponenter som fixeras på biologisk väg. Dessa icke-cementerade komponenter kräver bra benkvalitet för att fixeras på ett stabilt sätt, men har samtidigt visat sig ge bättre långtidsfixation än cementerade dito. Därför används de mer frekvent vid höftproteskirurgi hos unga patienter.

Protesdelarna i metall som insätts vid höftproteskirurgi är styvare än det omgivande benet. Det medför att det protesnära skelettet avlastas eftersom kraftöverföringen företrädesvis sker via den styvare metallkomponenten. Denna process fortgår kontinuerligt. Med tiden tunnas den skelettnära benmassan ut och en situation med artificiellt framkallad benskörhet uppkommer. Det är inte orimligt att tro att detta kan leda till ökad risk för protesnära fraktur i samband med ett framtida fall eller annat mindre trauma. Huruvida den protesnära benurkalkningen även kan bidra till ökad risk för lossning av proteskomponenterna är inte lika uppenbart ur teoretisk synvinkel, men icke desto mindre debatterat.

Mot bakgrund av ovanstående resonemang syftar studierna i denna avhandling till att belysa det kliniska och radiologiska resultatet vid höftproteskirurgi, med icke-cementerade proteskomponenter, efter såväl förstagångs- som om-operationer. Vidare syftar delarbetena III-V även till att belysa hur omfördelningen av den protesnära benmassan kan påverkas och motverkas, med hjälp av läkemedel samt design och ytskikt på protesdelarna.

Resultatet av studie I visar att om-operation av lossnade protesstammar kan utföras på ett säkert sätt, och med bra kliniskt resultat, med en icke-cementerad stam ämnad för förstagångsoperationer, om skelettet inte är kraftigt nedbrutet runt den lossnade stammen. Trots att den använda icke-cementerade stammen är designad för att överföra belastningen till skelettet företrädesvis i övre delen av lårbenet, och på så sätt verka benbesparande, uppfylls inte detta syfte fullt ut. I studie II visar bentäthetsmätningar av det protesnära skelettet omfattande förluster av benmineralmassa, framför allt runt övre delen av stammen, av skäl som ovan nämnts. Studie III visar att man kan minska benmineralurkalkningen i det protesnära skelettet, upp till ett år efter höftproteskirurgi, efter 6 månaders medicinering med osteoporosmedicinen bisfosfonat. I studie IV visas att en mycket kort kilformad design av en höftprotesstam kan minska den protesnära benmineralurkalkningen, upp till två efter höftproteskirurgi, jämfört med en konventionell stam. Slutligen, i

studie V, testas om en ny typ av titanyta på ledskålens baksida, kan minska den protesnära benmineralurkalkningen genom att öka beninväxten i den microskrovliga ytan. Denna hypotes kunde inte verifieras då benförlusterna bakom den nya typen av ledskål uppvisade samma mönster och samma omfattning som bakom en konventionell ledskål i titan. I studie V jämfördes även slitaget av plastledytan mellan den artificiella metallkulan och ledskålen i polyetylen. Slitageprodukter av polyetylen har visats ge bennedbrytning i det protesnära skelettet och bidrar därför till protesnära benförluster efter höftproteskirurgi. Vi fann ingen skillnad i slitage mellan en modern E-vitaminbehandlade, höggradigt slitagebeständig polyetylenplast och en konventionellt höggradigt slitagebeständig plast, upp till två efter operation. Däremot uppvisade E-vitaminplasten större hårdhet, då den deformerades i mindre omfattning under det första postoperativa året.

Sammanfattningsvis visar studierna i denna avhandling att protesnära benmineralförluster kan minskas med hjälp av farmakologi och protesdesign men inte säkert med ytstrukturer med ökad porositet. Om-operation av lösa höftprotesstammar kan utföras med bra kliniskt resultat med en ickecementerad stam, ämnad för första-gångsoperation, om bendefekterna i lårbenets övre del inte är omfattande. ⊙

14 ACKNOWLEDGEMENTS

This thesis has come to fruition because of the support of many people. To all my colleagues and to the staff at the Department of Orthopaedics at Danderyd Hospital, I would like to express my deepest thanks and heartfelt gratitude to you all, for supporting the work and effort that has gone into this thesis.

I would particularly like to express my sincere gratitude for all the help and support I have received from:

ANDRÉ STARK, my principal supervisor, for your support in every way, your never ending enthusiasm and for giving me the encouragement to complete this thesis

GUSTAF NEANDER AND ULF LILLKRONA, the present and former Heads of the Department of Orthopaedics at Danderyd Hospital, for giving me support and time to work on my thesis.

OLOF SKÖLDENBERG, my co-supervisor, for always being there when I needed your help and support, and for always being so good humored! I have learnt so much from you!!

OLLE MUREN, my co-supervisor, for always being a wise man and a very capable colleague. Thank you for invaluable input into my research!

TORBJÖRN AHL, my co-supervisor and mentor in Clinical Orthopaedics! I am so impressed by your curiosity, your enthusiasm and your boundless energy,. Still caring 100% for every patient!

HENRIK BODÉN, my co-author. Now it is my turn to express my deepest gratitude to you for being my room mate! You provide the perfect mix of an excellent working atmosphere, a nice chat and a good laugh!

GHAZI CHAMMOUT, AGATA RYSINSKA, THOMAS EISLER, my co-authors and esteemed colleagues at the Joint Replacement Unit at Danderyd Hospital. Thanks for being part of our group, on and off hours! You make it joyful to go to work.

PAULA KELLY-PETTERSSON AND HELENE SJÖÖ, our excellent research nurses, for providing splendid support and being the administrative "drive" in all my research! This thesis would not have been written without you, Paula!

TOVE ÖHRMAN AND ULF PETERSON, Medical Physicists, Department of Nuclear Medicine at Danderyd Hospital, for your patience and hard work in measuring the Dexa-examinations in study IV and V. My special thanks go also to all the staff at the Nuclear Medicine Department for your help in carrying out the examinations.

LISE-LOTTE WIDMARK AND EVA HOFMAN, for all your expert help in setting up the RSA-lab at Danderyd Hospital, and Lotta, for doing all the RSA-examinations in study IV and V.

LARS WEIDENHIELM, my mentor in research, for always showing interest in how my work progressed. Fortunately, the conditions at work very favourable for carrying out research and therefore, I did not need so much support. But I have enjoyed having a chat every now and then.

PER ADOLPHSON AND NILS DALÉN, my former supervisors (as time has elapsed, some changes have occurred…), thank you to you both for introducing me to the field of research.

ELIN JOHANSSON, ARNE MELANDER AND MIKAEL TUNEDAL, from DePuy Johnsson & Johnsson, for your help with RSA-labeling of the stems in study IV.

ANDERS HAHN from Biomet, for your help with RSA-labeling of the stems in study IV.

JAN HULTBERG from Zimmer for appreciated help.

MY FRIENDS, who I have neglected this year... Perhaps they do not even know what I have been up to?

MY BROTHERS AND THEIR FAMILIES, for providing help and support and "a good time" every now and then.

MY PARENTS, for your never-ending support, and for being great grandparents!
What would we have done without you and the support from Monica and Håkan, Ingolf and Ene?

MY BELOVED FAMILY, the true meaning of my life!
Jenny, you are my best friend and all my love!
Filip, Jakob, Sara, my wonderful children, let´s now have fun in Florida!

THIS THESIS was supported by grants from the following foundations: Ulla and Gustaf Ugglas Stiftelse, Åke Wiberg Stiftelse, Loo and Hans Ostermans Stiftelse, Sven Norén Foundation, The regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.
DePuy Johnsson & Johnsson foundation for clinical research.

References

15 REFERENCES

1. **(SHAR) SHAR.** Swedish Hip Arthroplasty Register (SHAR). Annual report 2011. 2011; Available from: www.shpr.se.
2. **Boden HS, Skoldenberg OG, Salemyr MO, Lundberg HJ, Adolphson PY.** Continuous bone loss around a tapered uncemented femoral stem: a long-term evaluation with DEXA. Acta Orthop. 2006;77(6):877-85.
3. **Schmidt R, Kress AM, Nowak M, Forst R, Nowak TE, Mueller LA.** Periacetabular cortical and cancellous bone mineral density loss after press-fit cup fixation: a prospective 7-year follow-up. J Arthroplasty. 2012;27(7):1358-63 e1. Epub 2012/01/10.
4. **(NARA) NARA.** Nordic Arthroplasty Register. Available from: www.nordicarthroplasty.gov.
5. **Albrektsson T, Branemark PI, Hansson HA, Lindstrom J.** Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand. 1981;52(2):155-70. Epub 1981/01/01.
6. **Hansson HA, Albrektsson T, Branemark PI.** Structural aspects of the interface between tissue and titanium implants. The Journal of prosthetic dentistry. 1983;50(1):108-13. Epub 1983/07/01.
7. **Ullmark G, Hallin G, Nilsson O, Ullmark G, Hallin G, Nilsson O.** Impacted corticocancellous allografts and cement for femoral revision of total hip arthroplasty using Lubinus and Charnley prostheses. J Arthroplasty. 2002;17(3):325-34.
8. **Lamberton TD, Kenny PJ, Whitehouse SL, Timperley AJ, Gie GA.** Femoral Impaction Grafting in Revision Total Hip Arthroplasty: A Follow-Up of 540 Hips. The Journal of Arthroplasty. 2011;26(8):1154-60.
9. **Ornstein E, Atroshi I, Franzen H, Johnsson R, Sandquist P, Sundberg M.** Early complications after one hundred and forty-four consecutive hip revisions with impacted morselized allograft bone and cement. J Bone Joint Surg Am. 2002;84-A(8):1323-8. Epub 2002/08/15.
10. **Kim YH, Kim JS, Park JW, Joo JH.** Periacetabular osteolysis is the problem in contemporary total hip arthroplasty in young patients. J Arthroplasty. 2012;27(1):74-81. Epub 2011/05/10.
11. **Hallan G, Lie SA, Havelin LI.** High wear rates and extensive osteolysis in 3 types of uncemented total hip arthroplasty: a review of the PCA, the Harris Galante and the Profile/Tri-Lock Plus arthroplasties with a minimum of 12 years median follow-up in 96 hips. Acta Orthop. 2006;77(4):575-84. Epub 2006/08/25.
12. **Harris WH.** The problem is osteolysis. Clin Orthop Relat Res. 1995(311):46-53. Epub 1995/02/01.
13. **Paprosky WG, Greidanus NV, Antoniou J.** Minimum 10-year-results of extensively porous-coated stems in revision hip arthroplasty. Clin Orthop Relat Res. 1999(369):230-42. Epub 1999/12/28.
14. **Raman R, Kamath RP, Parikh A, Angus PD.** Revision of cemented hip arthroplasty using a hydroxyapatite-ceramic-coated femoral component. J Bone Joint Surg Br. 2005;87(8):1061-7. Epub 2005/07/29.
15. **Reikeras O, Gunderson RB.** Excellent results with femoral revision surgery using an extensively hydroxyapatite-coated stem: 59 patients followed for 10-16 years. Acta Orthop. 2006;77(1):98-103. Epub 2006/03/18.
16. **Bohm P, Bischel O.** Femoral revision with the Wagner SL revision stem : evaluation of one hundred and twenty-nine revisions followed for a mean of 4.8 years. J Bone Joint Surg Am. 2001;83-A(7):1023-31. Epub 2001/07/14.
17. **Weeden SH, Paprosky WG.** Minimal 11-year follow-up of extensively porous-coated stems in femoral revision total hip arthroplasty. J Arthroplasty. 2002;17(4 Suppl 1):134-7. Epub 2002/06/18.
18. **Kelly SJ, Incavo SJ, Beynnon B.** The use of a hydroxyapatite-coated primary stem in revision total hip arthroplasty. J Arthroplasty. 2006;21(1):64-71. Epub 2006/02/01.
19. **Khanuja HS, Issa K, Naziri Q, Banerjee S, Delanois RE, Mont MA.** Results of a Tapered Proximally-Coated Primary Cementless Stem for Revision Hip Surgery. J Arthroplasty. 2013. Epub 2013/05/25.
20. **Salemyr MF, Skoldenberg OG, Boden HG, Ahl TE, Adolphson PY.** Good results with an uncemented proximally HA-coated stem in hip revision surgery: 62 hips followed for 2-13 years. Acta Orthop. 2008;79(2):184-93. Epub 2008/05/20.
21. **Wolff J.** Gesetz der Transformation der Knochen: Verlag von August Hirschwald, Berlin; 1892.
22. **Aldinger PR, Sabo D, Pritsch M, Thomsen M, Mau H, Ewerbeck V, et al.** Pattern of periprosthetic bone remodeling around stable uncemented tapered hip stems: a prospective 84-month follow-up study and a median 156-month cross-sectional study with DXA. Calcif Tissue Int. 2003;73(2):115-21. Epub 2003/10/21.
23. **Kroger H, Venesmaa P, Jurvelin J, Miettinen H, Suomalainen O, Alhava E.** Bone density at the proximal femur after total hip arthroplasty. Clin Orthop Relat Res. 1998(352):66-74. Epub 1998/07/25.
24. **Wright JM, Pellicci PM, Salvati EA, Ghelman B, Roberts MM, Koh JL.** Bone density adjacent to press-fit acetabular components. A prospective analysis with quantitative computed tomography. J Bone Joint Surg Am. 2001;83-A(4):529-36. Epub 2001/04/24.
25. **Penny JO, Brixen K, Varmarken JE, Ovesen O, Overgaard S.** Changes in bone mineral density of the acetabulum, femoral neck and femoral shaft, after hip resurfacing and total hip replacement: Two-year results from a randomised study. J Bone Joint Surg Br. 2012;94(8):1036-44. Epub 2012/07/31.
26. **Brodner W, Bitzan P, Lomoschitz F, Krepler P, Jankovsky R, Lehr S, et al.** Changes in bone mineral density in the proximal femur after cementless total hip arthroplasty. A five-year longitudinal study. J Bone Joint Surg Br. 2004;86(1):20-6. Epub 2004/02/10.
27. **Streit MR, Merle C, Clarius M, Aldinger PR.** Late peri-prosthetic femoral fracture as a major mode of failure in uncemented primary hip replacement. J Bone Joint Surg Br. 2011;93(2):178-83. Epub 2011/02/02.
28. **Lindahl H.** Epidemiology of periprosthetic femur fracture around a total hip arthroplasty. Injury. 2007;38(6):651-4. Epub 2007/05/05.
29. **Bhandari M, Bajammal S, Guyatt GH, Griffith L, Busse JW, Schunemann H, et al.** Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty. A meta-analysis. J Bone Joint Surg Am. 2005;87(2):293-301. Epub 2005/02/03.
30. **Skoldenberg OG, Salemyr MO, Boden HS, Ahl TE, Adolphson PY.** The effect of weekly risedronate on periprosthetic bone resorption following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am. 2011;93(20):1857-64. Epub 2011/10/21.

References

31. **Yamasaki S, Masuhara K, Yamaguchi K, Nakai T, Fuji T, Seino Y.** Risedronate reduces postoperative bone resorption after cementless total hip arthroplasty. Osteoporos Int. 2007;18(7):1009-15. Epub 2007/06/08.
32. **Arabmotlagh M, Pilz M, Warzecha J, Rauschmann M.** Changes of femoral periprosthetic bone mineral density 6 years after treatment with alendronate following total hip arthroplasty. J Orthop Res. 2009;27(2):183-8. Epub 2008/08/30.
33. **Rahmy AI, Gosens T, Blake GM, Tonino A, Fogelman I.** Periprosthetic bone remodelling of two types of uncemented femoral implant with proximal hydroxyapatite coating: a 3-year follow-up study addressing the influence of prosthesis design and preoperative bone density on periprosthetic bone loss. Osteoporos Int. 2004;15(4):281-9. Epub 2003/12/09.
34. **Van der Wal BC, Rahmy AI, Grimm B, Blake GM, Heyligers IC, Tonino AJ.** The influence of implant design on periprosthetic bone remodelling of two types of uncemented HA-coated hip stems. A two-year follow-up study using DEXA. Hip Int. 2006;16(1):8-17. Epub 2006/01/01.
35. **Lerch M, von der Haar-Tran A, Windhagen H, Behrens BA, Wefstaedt P, Stukenborg-Colsman CM.** Bone remodelling around the Metha short stem in total hip arthroplasty: a prospective dual-energy X-ray absorptiometry study. Int Orthop. 2011. Epub 2011/09/22.
36. **Soballe K, Overgaard S, Hansen ES, Brokstedt-Rasmussen H, Lind M, Bunger C.** A review of ceramic coatings for implant fixation. Journal of long-term effects of medical implants. 1999;9(1-2):131-51. Epub 1999/10/28.
37. **Bobyn JD, Toh KK, Hacking SA, Tanzer M, Krygier JJ.** Tissue response to porous tantalum acetabular cups: a canine model. J Arthroplasty. 1999;14(3):347-54. Epub 1999/04/29.
38. **Galante J, Rostoker W, Lueck R, Ray RD.** Sintered fiber metal composites as a basis for attachment of implants to bone. J Bone Joint Surg Am. 1971;53(1):101-14. Epub 1971/01/01.
39. **Pilliar RM, Cameron HU, Macnab I.** Porous surface layered prosthetic devices. Biomedical engineering. 1975;10(4):126-31. Epub 1975/04/01.
40. **Harris WH.** Osteolysis and particle disease in hip replacement. A review. Acta Orthop Scand. 1994;65(1):113-23. Epub 1994/02/01.
41. **Harris WH.** Wear and periprosthetic osteolysis: the problem. Clin Orthop Relat Res. 2001(393):66-70. Epub 2002/01/05.
42. **Sochart DH.** Relationship of acetabular wear to osteolysis and loosening in total hip arthroplasty. Clin Orthop Relat Res. 1999(363):135-50. Epub 1999/06/24.
43. **McAuley JP, Culpepper WJ, Engh CA.** Total hip arthroplasty. Concerns with extensively porous coated femoral components. Clin Orthop Relat Res. 1998(355):182-8. Epub 1999/01/26.
44. **Engh CA, Jr.,** Young AM, Engh CA, Sr., Hopper RH, Jr. Clinical consequences of stress shielding after porous-coated total hip arthroplasty. Clin Orthop Relat Res. 2003(417):157-63. Epub 2003/12/04.
45. **Thanner J, Karrholm J, Malchau H, Herberts P.** Poor outcome of the PCA and Harris-Galante hip prostheses. Randomized study of 171 arthroplasties with 9-year follow-up. Acta Orthop Scand. 1999;70(2):155-62. Epub 1999/06/15.
46. **Orishimo KF, Claus AM, Sychterz CJ, Engh CA.** Relationship between polyethylene wear and osteolysis in hips with a second-generation porous-coated cementless cup after seven years of follow-up. J Bone Joint Surg Am. 2003;85-A(6):1095-9. Epub 2003/06/05.
47. **Dumbleton JH, Manley MT, Edidin AA.** A literature review of the association between wear rate and osteolysis in total hip arthroplasty. J Arthroplasty. 2002;17(5):649-61. Epub 2002/08/09.
48. **Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al.** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282(14):1344-52. Epub 1999/10/20.
49. **McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al.** Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344(5):333-40. Epub 2001/02/15.
50. **Bilezikian JP.** Efficacy of bisphosphonates in reducing fracture risk in postmenopausal osteoporosis. The American journal of medicine. 2009;122(2 Suppl):S14-21. Epub 2009/02/21.
51. **Jansen JP, Bergman GJD, Huels J, Olson M.** The Efficacy of Bisphosphonates in the Prevention of Vertebral, Hip, and Nonvertebral-Nonhip Fractures in Osteoporosis: A Network Meta-Analysis. Seminars in Arthritis and Rheumatism. 2011;40(4):275-84.e2.
52. **Venesmaa PK, Kroger HP, Miettinen HJ, Jurvelin JS, Suomalainen OT, Alhav EM.** Alendronate reduces periprosthetic bone loss after uncemented primary total hip arthroplasty: a prospective randomized study. J Bone Miner Res. 2001;16(11):2126-31. Epub 2001/11/08.
53. **Lin T, Yan SG, Cai XZ, Ying ZM.** Bisphosphonates for periprosthetic bone loss after joint arthroplasty: a meta-analysis of 14 randomized controlled trials. Osteoporos Int. 2012;23(6):1823-34. Epub 2011/09/21.
54. **Hilding M, Ryd L, Toksvig-Larsen S, Aspenberg P.** Clodronate prevents prosthetic migration: a randomized radiostereometric study of 50 total knee patients. Acta Orthop Scand. 2000;71(6):553-7. Epub 2001/01/06.
55. **Friedl G, Radl R, Stihsen C, Rehak P, Aigner R, Windhager R.** The effect of a single infusion of zoledronic acid on early implant migration in total hip arthroplasty. A randomized, double-blind, controlled trial. J Bone Joint Surg Am. 2009;91(2):274-81. Epub 2009/02/03.
56. **Williams DF.** Definitions in biomaterials. Progress in biomedical engineering.: Elsevier Science Publishers, B.V., Amsterdam, New York; 1987.
57. **Cohen J, Wulff J.** Clinical Failure Caused by Corrosion of a Vitallium Plate CASE REPORT, NEW TESTING METHODS FOR CREVICE CORROSION, AND NEW TECHNIQUES FOR FASHIONING COBALT CHROMIUM ALLOYS TO BE USED IN SURGICAL IMPLANTS. The Journal of Bone & Joint Surgery. 1972;54(3):617-28.
58. **Head WC, Bauk DJ, Emerson RH, Jr.** Titanium as the material of choice for cementless femoral components in total hip arthroplasty. Clin Orthop Relat Res. 1995(311):85-90. Epub 1995/02/01.
59. **Meding JB, Keating EM, Ritter MA, Faris PM, Berend ME.** Minimum ten-year follow-up of a straight-stemmed, plasma-sprayed, titanium-alloy, uncemented femoral component in primary total hip arthroplasty. J Bone Joint Surg Am. 2004;86-A(1):92-7. Epub 2004/01/09.
60. **Spotorno L, Romagnoli S, Ivaldo N, Grappiolo G, Bibbiani E, Blaha DJ, et al.** The CLS system. Theoretical concept and results. Acta Orthop Belg. 1993;59 Suppl 1:144-8. Epub 1993/01/01.
61. **Vervest TM, Anderson PG, Van Hout F, Wapstra FH, Louwerse RT, Koetsier JW.** Ten to twelve-year re-

sults with the Zweymuller cementless total hip prosthesis. J Arthroplasty. 2005;20(3):362-8. Epub 2005/04/06.

62. **Karageorgiou V, Kaplan D.** Porosity of 3D biomaterial scaffolds and osteogenesis. Biomaterials. 2005;26(27):5474-91. Epub 2005/04/30.
63. **Bobyn JD, Stackpool GJ, Hacking SA, Tanzer M, Krygier JJ.** Characteristics of bone ingrowth and interface mechanics of a new porous tantalum biomaterial. J Bone Joint Surg Br. 1999;81(5):907-14. Epub 1999/10/26.
64. **Thomas KA, Kay JF, Cook SD, Jarcho M.** The effect of surface macrotexture and hydroxylapatite coating on the mechanical strengths and histologic profiles of titanium implant materials. Journal of biomedical materials research. 1987;21(12):1395-414. Epub 1987/12/01.
65. **Soballe K, Hansen ES, H BR, Jorgensen PH, Bunger C.** Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions. J Orthop Res. 1992;10(2):285-99. Epub 1992/03/01.
66. **Soballe K, Hansen ES, Brockstedt-Rasmussen H, Hjortdal VE, Juhl GI, Pedersen CM, et al.** Gap healing enhanced by hydroxyapatite coating in dogs. Clin Orthop Relat Res. 1991(272):300-7. Epub 1991/11/01.
67. **Soballe K, Hansen ES, Brockstedt-Rasmussen H, Pedersen CM, Bunger C.** Bone graft incorporation around titanium-alloy- and hydroxyapatite-coated implants in dogs. Clin Orthop Relat Res. 1992(274):282-93. Epub 1992/01/01.
68. **Pilliar RM, Lee JM, Maniatopoulos C.** Observations on the effect of movement on bone ingrowth into porous-surfaced implants. Clin Orthop Relat Res. 1986(208):108-13. Epub 1986/07/01.
69. **Soballe K, Hansen ES, Brockstedt-Rasmussen H, Bunger C.** Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. J Bone Joint Surg Br. 1993;75(2):270-8. Epub 1993/03/01.
70. **Rahbek O, Overgaard S, Jensen TB, Bendix K, Soballe K.** Sealing effect of hydroxyapatite coating: a 12-month study in canines. Acta Orthop Scand. 2000;71(6):563-73. Epub 2001/01/06.
71. **Rahbek O, Overgaard S, Lind M, Bendix K, Bunger C, Soballe K.** Sealing effect of hydroxyapatite coating on peri-implant migration of particles. An experimental study in dogs. J Bone Joint Surg Br. 2001;83(3):441-7. Epub 2001/05/09.
72. **Moilanen T, Stocks GW, Freeman MA, Scott G, Goodier WD, Evans SJ.** Hydroxyapatite coating of an acetabular prosthesis. Effect on stability. J Bone Joint Surg Br. 1996;78(2):200-5. Epub 1996/03/01.
73. **Soballe K, Toksvig-Larsen S, Gelineck J, Fruensgaard S, Hansen ES, Ryd L, et al.** Migration of hydroxyapatite coated femoral prostheses. A Roentgen Stereophotogrammetric study. J Bone Joint Surg Br. 1993;75(5):681-7. Epub 1993/09/01.
74. **Thanner J.** The acetabular component in total hip arthroplasty. Evaluation of different fixation principles. Acta orthopaedica Scandinavica Supplementum. 1999;286:1-41. Epub 1999/11/26.
75. **Lee JM, Lee CW.** Comparison of hydroxyapatite-coated and non-hydroxyapatite-coated noncemented total hip arthroplasty in same patients. J Arthroplasty. 2007;22(7):1019-23. Epub 2007/10/09.
76. **Paulsen A, Pedersen AB, Johnsen SP, Riis A, Lucht U, Overgaard S.** Effect of hydroxyapatite coating on risk of revision after primary total hip arthroplasty in younger patients: findings from the Danish Hip Arthroplasty Registry. Acta Orthop. 2007;78(5):622-8. Epub 2007/10/30.
77. **Lazarinis S, Karrholm J, Hailer NP.** Effects of hydroxyapatite coating on survival of an uncemented femoral stem. A Swedish Hip Arthroplasty Register study on 4,772 hips. Acta Orthop. 2011;82(4):399-404. Epub 2011/07/15.
78. **Lazarinis S, Karrholm J, Hailer NP.** Increased risk of revision of acetabular cups coated with hydroxyapatite. Acta Orthop. 2010;81(1):53-9. Epub 2009/12/09.
79. **Rokkum M, Reigstad A, Johansson CB.** HA particles can be released from well-fixed HA-coated stems: histopathology of biopsies from 20 hips 2-8 years after implantation. Acta Orthop Scand. 2002;73(3):298-306. Epub 2002/07/30.
80. **Bloebaum RD, Beeks D, Dorr LD, Savory CG, DuPont JA, Hofmann AA.** Complications with hydroxyapatite particulate separation in total hip arthroplasty. Clin Orthop Relat Res. 1994(298):19-26. Epub 1994/01/01.
81. **Kim SY, Kim DH, Kim YG, Oh CW, Ihn JC.** Early failure of hemispheric hydroxyapatite-coated acetabular cups. Clin Orthop Relat Res. 2006;446:233-8. Epub 2006/05/25.
82. **Chang JK, Chen CH, Huang KY, Wang GJ.** Eight-year results of hydroxyapatite-coated hip arthroplasty. J Arthroplasty. 2006;21(4):541-6. Epub 2006/06/20.
83. **Kuzyk PR, Saccone M, Sprague S, Simunovic N, Bhandari M, Schemitsch EH.** Cross-linked versus conventional polyethylene for total hip replacement: a meta-analysis of randomised controlled trials. J Bone Joint Surg Br. 2011;93(5):593-600. Epub 2011/04/23.
84. **Kurtz SM, Muratoglu OK, Evans M, Edidin AA.** Advances in the processing, sterilization, and crosslinking of ultra-high molecular weight polyethylene for total joint arthroplasty. Biomaterials. 1999;20(18):1659-88. Epub 1999/09/30.
85. **McKellop H, Shen FW, Lu B, Campbell P, Salovey R.** Development of an extremely wear-resistant ultra high molecular weight polyethylene for total hip replacements. J Orthop Res. 1999;17(2):157-67. Epub 1999/04/30.
86. **Rohrl SM, Li MG, Nilsson KG, Nivbrant B.** Very low wear of non-remelted highly cross-linked polyethylene cups: an RSA study lasting up to 6 years. Acta Orthop. 2007;78(6):739-45. Epub 2008/02/01.
87. **Digas G, Karrholm J, Thanner J, Malchau H, Herberts P.** Highly cross-linked polyethylene in cemented THA: randomized study of 61 hips. Clin Orthop Relat Res. 2003(417):126-38. Epub 2003/12/04.
88. **Digas G, Karrholm J, Thanner J, Herberts P.** 5-year experience of highly cross-linked polyethylene in cemented and uncemented sockets: two randomized studies using radiostereometric analysis. Acta Orthop. 2007;78(6):746-54. Epub 2008/02/01.
89. **McKellop H, Shen FW, Lu B, Campbell P, Salovey R.** Effect of sterilization method and other modifications on the wear resistance of acetabular cups made of ultra-high molecular weight polyethylene. A hip-simulator study. J Bone Joint Surg Am. 2000;82-A(12):1708-25. Epub 2000/12/29.
90. **Oral E, Christensen SD, Malhi AS, Wannomae KK, Muratoglu OK.** Wear resistance and mechanical properties of highly cross-linked, ultra-high-molecular weight polyethylene doped with vitamin E. J Arthroplasty. 2006;21(4):580-91. Epub 2006/06/20.
91. **Sychterz CJ, Engh CA, Yang A.** Analysis of temporal wear patterns of porous-coated acetabular components: Distinguishing between true wear and so-called bedding-in. Journal of Bone and Joint Surgery - Series A. 1999;81(6):821-30.
92. **Callary SA, Campbell DG, Mercer G, Nilsson KG, Field JR.** Wear of a 5 Megarad Cross-linked Polyethylene Liner: A 6-year RSA Study. Clin Or-

thop Relat Res. 2013;471(7):2238-44. Epub 2013/01/22.

93. **Zhou ZK, Li MG, Borlin N, Wood DJ, Nivbrant B.** No increased migration in cups with ceramic-on-ceramic bearing: an RSA study. Clin Orthop Relat Res. 2006;448:39-45. Epub 2006/07/11.
94. **Dorr LD, Faugere MC, Mackel AM, Gruen TA, Bognar B, Malluche HH.** Structural and cellular assessment of bone quality of proximal femur. Bone. 1993;14(3):231-42. Epub 1993/05/01.
95. **Santori N, Albanese CV, Learmonth ID, Santori FS.** Bone preservation with a conservative metaphyseal loading implant. Hip Int. 2006;16 Suppl 3:16-21. Epub 2006/01/01.
96. **Walker PS CS, Hua J, Huirhead-Alwood SK, Bentley G.** The effect of a lateral flare feature on uncemented hip stems. hip International. 1999(9):71-80.
97. **Renkawitz T, Santori FS, Grifka J, Valverde C, Morlock MM, Learmonth ID.** A new short uncemented, proximally fixed anatomic femoral implant with a prominent lateral flare: design rationals and study design of an international clinical trial. BMC Musculoskelet Disord. 2008;9:147. Epub 2008/11/06.
98. **Toth K, Mecs L, Kellermann P.** Early experience with the Depuy Proxima short stem in total hip arthroplasty. Acta Orthop Belg. 2010;76(5):613-8. Epub 2010/12/09.
99. **Ghera S, Pavan L.** The DePuy Proxima hip: a short stem for total hip arthroplasty. Early experience and technical considerations. Hip Int. 2009;19(3):215-20. Epub 2009/10/02.
100. **Oral E, Muratoglu OK.** Vitamin E diffused, highly crosslinked UHMWPE: a review. Int Orthop. 2011;35(2):215-23. Epub 2010/12/02.
101. **(AOA) AOA.** Australian Orthopaedic Association National Joint Replacement Registry. Available from: https://aoanjrr.dmac.adelaide.edu.au.
102. **Moore AT.** The self-locking metal hip prosthesis. J Bone Joint Surg Am. 1957;39-A(4):811-27. Epub 1957/07/01.
103. **Kwon MS, Kuskowski M, Mulhall KJ, Macaulay W, Brown TE, Saleh KJ.** Does surgical approach affect total hip arthroplasty dislocation rates? Clin Orthop Relat Res. 2006;447:34-8. Epub 2006/06/03.
104. **(SOA).** SOA. Svensk Ortopedisk Förenings skriftserie nr 18, 2006. 2006.
105. **Gustilo RB, Pasternak HS.** Revision total hip arthroplasty with titanium ingrowth prosthesis and bone grafting for failed cemented femoral component loosening. Clin Orthop Relat Res. 1988(235):111-9. Epub 1988/10/01.
106. **Engelbrecht E, Siegel A.** [Complications following hip joint prosthesis]. Radiologe. 1989;29(10):508-18. Epub 1989/10/01. Komplikationen nach Huftgelenksendoprothesen.
107. **Engh CA, Massin P, Suthers KE.** Roentgenographic assessment of the biologic fixation of porous-surfaced femoral components. Clin Orthop Relat Res. 1990(257):107-28. Epub 1990/08/01.
108. **Malchau H, Karrholm J, Wang YX, Herberts P.** Accuracy of migration analysis in hip arthroplasty. Digitized and conventional radiography, compared to radiostereometry in 51 patients. Acta Orthop Scand. 1995;66(5):418-24. Epub 1995/10/01.
109. **Brooker AF, Bowerman JW, Robinson RA, Riley LH, Jr.** Ectopic ossification following total hip replacement. Incidence and a method of classification. J Bone Joint Surg Am. 1973;55(8):1629-32. Epub 1973/12/01.
110. **Krismer M, Bauer R, Tschupik J, Mayrhofer P.** EBRA: a method to measure migration of acetabular components. J Biomech. 1995;28(10):1225-36. Epub 1995/10/01.
111. **Biedermann R, Krismer M, Stockl B, Mayrhofer P, Ornstein E, Franzen H.** Accuracy of EBRA-FCA in the measurement of migration of femoral components of total hip replacement. Einzel-Bild-Rontgen-Analyse-femoral component analysis. J Bone Joint Surg Br. 1999;81(2):266-72. Epub 1999/04/16.
112. **Krismer M, Biedermann R, Stockl B, Fischer M, Bauer R, Haid C.** The prediction of failure of the stem in THR by measurement of early migration using EBRA-FCA. Einzel-Bild-Roentgen-Analyse-femoral component analysis. J Bone Joint Surg Br. 1999;81(2):273-80. Epub 1999/04/16.
113. **Selvik G.** Roentgen stereophotogrammetry. A method for the study of the kinematics of the skeletal system. Acta orthopaedica Scandinavica Supplementum. 1989;232:1-51. Epub 1989/01/01.
114. **Karrholm J, Borssen B, Lowenhielm G, Snorrason F.** Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses. J Bone Joint Surg Br. 1994;76(6):912-7. Epub 1994/11/01.
115. **Karrholm J.** Radiostereometric analysis of early implant migration - a valuable tool to ensure proper introduction of new implants. Acta Orthop. 2012;83(6):551-2. Epub 2012/11/07.
116. **Nieuwenhuijse MJ, Valstar ER, Kaptein BL, Nelissen RG.** Good diagnostic performance of early migration as a predictor of late aseptic loosening of acetabular cups: results from ten years of follow-up with Roentgen stereophotogrammetric analysis (RSA). J Bone Joint Surg Am. 2012;94(10):874-80. Epub 2012/05/24.
117. **Pijls BG, Nieuwenhuijse MJ, Fiocco M, Plevier JW, Middeldorp S, Nelissen RG, et al.** Early proximal migration of cups is associated with late revision in THA: a systematic review and meta-analysis of 26 RSA studies and 49 survivalstudies. Acta Orthop. 2012;83(6):583-91. Epub 2012/11/07.
118. **Valstar ER, Vrooman HA, Toksvig-Larsen S, Ryd L, Nelissen RG.** Digital automated RSA compared to manually operated RSA. J Biomech. 2000;33(12):1593-9. Epub 2000/09/28.
119. **Borlin N, Rohrl SM, Bragdon CR.** RSA wear measurements with or without markers in total hip arthroplasty. J Biomech. 2006;39(9):1641-50. Epub 2005/07/02.
120. **Soderkvist I, Wedin PA.** Determining the movements of the skeleton using well-configured markers. J Biomech. 1993;26(12):1473-7. Epub 1993/12/01.
121. **Valstar ER, Gill R, Ryd L, Flivik G, Börlin N, Kärrholm J.** Guidelines for standardization of radiostereometry (RSA) of implants. acta orthopaedica. 2005;76(4):563-72.
122. **Mortimer ES, Rosenthall L, Paterson I, Bobyn JD.** Effect of rotation on periprosthetic bone mineral measurements in a hip phantom. Clin Orthop Relat Res. 1996(324):269-74. Epub 1996/03/01.
123. **Mazess R, Collick B, Trempe J, Barden H, Hanson J.** Performance evaluation of a dual-energy x-ray bone densitometer. Calcif Tissue Int. 1989;44(3):228-32. Epub 1989/03/01.
124. **Kilgus DJ, Shimaoka EE, Tipton JS, Eberle RW.** Dual-energy X-ray absorptiometry measurement of bone mineral density around porous-coated cementless femoral implants. Methods and preliminary results. J Bone Joint Surg Br. 1993;75(2):279-87. Epub 1993/03/01.
125. **Gruen TA, McNeice GM, Amstutz HC.** "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. Clin Orthop Relat Res. 1979(141):17-27. Epub 1979/06/01.
126. **Wilkinson JM, Peel NF, Elson RA, Stockley I, Eastell R.** Measuring bone mineral density of the pelvis and proximal femur after total hip arthroplasty. J Bone Joint Surg Br. 2001;83(2):283-8.

Epub 2001/04/04.

127. Laursen MB, Nielsen PT, Soballe K. DXA scanning of acetabulum in patients with cementless total hip arthroplasty. J Clin Densitom. 2005;8(4):476-83. Epub 2005/11/29.

128. DeLee JG, Charnley J. Radiological demarcation of cemented sockets in total hip replacement. Clin Orthop Relat Res. 1976(121):20-32. Epub 1976/11/01.

129. Nishii T, Sugano N, Masuhara K, Shibuya T, Ochi T, Tamura S. Longitudinal evaluation of time related bone remodeling after cementless total hip arthroplasty. Clin Orthop Relat Res. 1997(339):121-31. Epub 1997/06/01.

130. Charnley J. The long-term results of low-friction arthroplasty of the hip performed as a primary intervention. J Bone Joint Surg Br. 1972;54(1):61-76. Epub 1972/02/01.

131. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am. 1969;51(4):737-55. Epub 1969/06/01.

132. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-40. Epub 1988/12/01.

133. Bellamy N. Outcome measurement in osteoarthritis clinical trials. The Journal of rheumatology Supplement. 1995;43:49-51. Epub 1995/02/01.

134. Soderman P, Malchau H. Is the Harris hip score system useful to study the outcome of total hip replacement? Clin Orthop Relat Res. 2001(384):189-97. Epub 2001/03/16.

135. National Joint Registry. Available from: www.njrcentre.org.uk.

136. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine. 2001;33(5):337-43. Epub 2001/08/09.

137. Mahon JL, Bourne RB, Rorabeck CH, Feeny DH, Stitt L, Webster-Bogaert S. Health-related quality of life and mobility of patients awaiting elective total hip arthroplasty: a prospective study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2002;167(10):1115-21. Epub 2002/11/13.

138. Montin L, Suominen T, Katajisto J, Lepisto J, Leino-Kilpi H. Economic outcomes from patients' perspective and health-related quality of life after total hip arthroplasty. Scand J Caring Sci. 2009;23(1):11-20. Epub 2009/03/03.

139. Alm JJ, Makinen TJ, Lankinen P, Moritz N, Vahlberg T, Aro HT. Female patients with low systemic BMD are prone to bone loss in Gruen zone 7 after cementless total hip arthroplasty. Acta Orthop. 2009;80(5):531-7. Epub 2009/11/18.

140. Kiratli BJ, Checovich MM, McBeath AA, Wilson MA, Heiner JP. Measurement of bone mineral density by dual-energy x-ray absorptiometry in patients with the Wisconsin hip, an uncemented femoral stem. J Arthroplasty. 1996;11(2):184-93. Epub 1996/02/01.

141. Baad-Hansen T, Kold S, Nielsen PT, Laursen MB, Christensen PH, Soballe K. Comparison of trabecular metal cups and titanium fiber-mesh cups in primary hip arthroplasty: a randomized RSA and bone mineral densitometry study of 50 hips. Acta Orthop. 2011;82(2):155-60. Epub 2011/03/26.

142. Skoldenberg OG, Boden HS, Salemyr MO, Ahl TE, Adolphson PY. Periprosthetic proximal bone loss after uncemented hip arthroplasty is related to stem size: DXA measurements in 138 patients followed for 2-7 years. Acta Orthop. 2006;77(3):386-92.

143. Mulliken BD, Rorabeck CH, Bourne RB. Uncemented revision total hip arthroplasty: a 4-to-6-year review. Clin Orthop Relat Res. 1996(325):156-62. Epub 1996/04/01.

144. Malkani AL, Lewallen DG, Cabanela ME, Wallrichs SL. Femoral component revision using an uncemented, proximally coated, long-stem prosthesis. J Arthroplasty. 1996;11(4):411-8. Epub 1996/06/01.

145. Boden H, Salemyr M, Skoldenberg O, Ahl T, Adolphson P. Total hip arthroplasty with an uncemented hydroxyapatite-coated tapered titanium stem: results at a minimum of 10 years' follow-up in 104 hips. J Orthop Sci. 2006;11(2):175-9. Epub 2006/03/29.

146. Soballe K. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs. Acta orthopaedica Scandinavica Supplementum. 1993;255:1-58. Epub 1993/01/01.

147. Coathup MJ, Blunn GW, Flynn N, Williams C, Thomas NP. A comparison of bone remodelling around hydroxyapatite-coated, porous-coated and grit-blasted hip replacements retrieved at post-mortem. J Bone Joint Surg Br. 2001;83(1):118-23. Epub 2001/03/14.

148. Jacobs JJ, Sumner DR, Galante JO. Mechanisms of bone loss associated with total hip replacement. The Orthopedic clinics of North America. 1993;24(4):583-90. Epub 1993/10/01.

149. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. J Bone Joint Surg Am. 1992;74(6):849-63. Epub 1992/07/01.

150. Daugaard H, Elmengaard B, Bechtold JE, Jensen T, Soballe K. The effect on bone growth enhancement of implant coatings with hydroxyapatite and collagen deposited electrochemically and by plasma spray. Journal of biomedical materials research Part A. 2010;92(3):913-21. Epub 2009/03/18.

151. Boe BG, Rohrl SM, Heier T, Snorrason F, Nordsletten L. A prospective randomized study comparing electrochemically deposited hydroxyapatite and plasma-sprayed hydroxyapatite on titanium stems. Acta Orthop. 2011;82(1):13-9. Epub 2010/12/30.

152. Lazarinis S, Karrholm J, Hailer NP. Effects of hydroxyapatite coating of cups used in hip revision arthroplasty. Acta Orthop. 2012;83(5):427-35. Epub 2012/09/04.

153. Collier JP, Sutula LC, Currier BH, Currier JH, Wooding RE, Williams IR, et al. Overview of polyethylene as a bearing material: comparison of sterilization methods. Clin Orthop Relat Res. 1996(333):76-86. Epub 1996/12/01.

154. Sychterz CJ, Orishimo KF, Engh CA. Sterilization and polyethylene wear: clinical studies to support laboratory data. J Bone Joint Surg Am. 2004;86-A(5):1017-22. Epub 2004/05/01.

155. Bracco P, Oral E. Vitamin E-stabilized UHMWPE for total joint implants: a review. Clin Orthop Relat Res. 2011;469(8):2286-93. Epub 2010/12/07.

156. Oral E, Ghali BW, Neils A, Muratoglu OK. A new mechanism of oxidation in ultrahigh molecular weight polyethylene caused by squalene absorption. Journal of biomedical materials research Part B, Applied biomaterials. 2012;100(3):742-51. Epub 2011/12/23.

157. Shaver SM, Brown TD, Hillis SL, Callaghan JJ. Digital edge-detection measurement of polyethylene wear after total hip arthroplasty. J Bone Joint Surg Am. 1997;79(5):690-700. Epub 1997/05/01.

158. Sychterz CJ, Engh CA, Jr., Swope SW, McNulty DE, Engh CA. Analysis of prosthetic femoral heads retrieved at autopsy. Clin Orthop Relat Res.

1999(358):223-34. Epub 1999/02/12.
159. **Wilkinson JM, Hamer AJ, Elson RA, Stockley I, Eastell R.** Precision of EBRA-Digital software for monitoring implant migration after total hip arthroplasty. J Arthroplasty. 2002;17(7):910-6. Epub 2002/10/11.
160. **Biedermann R, Stockl B, Krismer M, Mayrhofer P, Ornstein E, Franzen H.** Evaluation of accuracy and precision of bone markers for the measurement of migration of hip prostheses. A comparison of conventional measurements. J Bone Joint Surg Br. 2001;83(5):767-71. Epub 2001/07/31.
161. **Onsten I, Berzins A, Shott S, Sumner DR.** Accuracy and precision of radiostereometric analysis in the measurement of THR femoral component translations: human and canine in vitro models. J Orthop Res. 2001;19(6):1162-7. Epub 2002/01/10.
162. **Bragdon CR, Malchau H, Yuan X, Perinchief R, Karrholm J, Borlin N, et al.** Experimental assessment of precision and accuracy of radiostereometric analysis for the determination of polyethylene wear in a total hip replacement model. J Orthop Res. 2002;20(4):688-95. Epub 2002/08/10.
163. **Borlin N, Thien T, Karrholm J.** The precision of radiostereometric measurements. Manual vs. digital measurements. J Biomech. 2002;35(1):69-79. Epub 2001/12/19.
164. **Kaptein BL, Valstar ER, Stoel BC, Rozing PM, Reiber JH.** A new model-based RSA method validated using CAD models and models from reversed engineering. J Biomech. 2003;36(6):873-82. Epub 2003/05/14.
165. **Kaptein BL, Valstar ER, Spoor CW, Stoel BC, Rozing PM.** Model-based RSA of a femoral hip stem using surface and geometrical shape models. Clin Orthop Relat Res. 2006;448:92-7. Epub 2006/07/11.
166. **Livermore J, Ilstrup D, Morrey B.** Effect of femoral head size on wear of the polyethylene acetabular component. J Bone Joint Surg Am. 1990;72(4):518-28. Epub 1990/04/01.
167. **Martell JM, Berdia S.** Determination of polyethylene wear in total hip replacements with use of digital radiographs. Journal of Bone and Joint Surgery - Series A. 1997;79(11):1635-41.
168. **Devane PA, Bourne RB, Rorabeck CH, Hardie RM, Horne JG.** Measurement of polyethylene wear in metal-backed acetabular cups. I. Three-dimensional technique. Clin Orthop Relat Res. 1995(319):303-16. Epub 1995/10/01.
169. **Stilling M, Kold S, de Raedt S, Andersen NT, Rahbek O, Soballe K.** Superior accuracy of model-based radiostereometric analysis for measurement of polyethylene wear: A phantom study. Bone & joint research. 2012;1(8):180-91. Epub 2013/04/24.
170. **Engh CA, Jr.,** McAuley JP, Sychterz CJ, Sacco ME, Engh CA, Sr. The accuracy and reproducibility of radiographic assessment of stress-shielding. A postmortem analysis. J Bone Joint Surg Am. 2000;82-A(10):1414-20. Epub 2000/11/01.
171. **Kroger H, Miettinen H, Arnala I, Koski E, Rushton N, Suomalainen O.** Evaluation of periprosthetic bone using dual-energy x-ray absorptiometry: precision of the method and effect of operation on bone mineral density. J Bone Miner Res. 1996;11(10):1526-30. Epub 1996/10/01.
172. **Martini F, Kremling E, Schmidt B, Sell S, Mayer F.** Bone mineral density of the proximal femur after unilateral cementless total hip replacement. Int Orthop. 1999;23(2):104-6. Epub 1999/07/28.
173. **Cohen B, Rushton N.** Accuracy of DEXA measurement of bone mineral density after total hip arthroplasty. J Bone Joint Surg Br. 1995;77(3):479-83. Epub 1995/05/01.
174. **Kim YH, Choi Y, Kim JS.** Comparison of bone mineral density changes around short, metaphyseal-fitting, and conventional cementless anatomical femoral components. J Arthroplasty. 2011;26(6):931-40 e1. Epub 2010/12/07.
175. **Albanese CV, Santori FS, Pavan L, Learmonth ID, Passariello R.** Periprosthetic DXA after total hip arthroplasty with short vs. ultra-short custom-made femoral stems: 37 patients followed for 3 years. Acta Orthop. 2009;80(3):291-7. Epub 2009/06/30.
176. **Decking R, Rokahr C, Zurstegge M, Simon U, Decking J.** Maintenance of bone mineral density after implantation of a femoral neck hip prosthesis. BMC Musculoskelet Disord. 2008;9:17. Epub 2008/02/02.
177. **Digas G, Karrholm J, Thanner J.** Different loss of BMD using uncemented press-fit and whole polyethylene cups fixed with cement: repeated DXA studies in 96 hips randomized to 3 types of fixation. Acta Orthop. 2006;77(2):218-26. Epub 2006/06/06.
178. **Mueller LA, Kress A, Nowak T, Pfander D, Pitto RP, Forst R, et al.** Periacetabular bone changes after uncemented total hip arthroplasty evaluated by quantitative computed tomography. acta orthopaedica. 2006;77(3):380-5.
179. **Boden H, Adolphson P.** No adverse effects of early weight bearing after uncemented total hip arthroplasty: a randomized study of 20 patients. Acta Orthop Scand. 2004;75(1):21-9. Epub 2004/03/17.
180. **Kalender WA.** Effective dose values in bone mineral measurements by photon absorptiometry and computed tomography. Osteoporos Int. 1992;2(2):82-7. Epub 1992/03/01.
181. **Fries JF, Spitz PW, Young DY.** The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol. 1982;9(5):789-93. Epub 1982/09/01.
182. **van der Wal BC, Rahmy A, Grimm B, Heyligers I, Tonino A.** Preoperative bone quality as a factor in dual-energy X-ray absorptiometry analysis comparing bone remodelling between two implant types. Int Orthop. 2008;32(1):39-45. Epub 2006/11/07.
183. **Khanuja HS, Vakil JJ, Goddard MS, Mont MA.** Cementless femoral fixation in total hip arthroplasty. J Bone Joint Surg Am. 2011;93(5):500-9. Epub 2011/03/04.
184. **Engh CA, Bobyn JD, Glassman AH.** Porous-coated hip replacement. The factors governing bone ingrowth, stress shielding, and clinical results. J Bone Joint Surg Br. 1987;69(1):45-55. Epub 1987/01/01.
185. **Engh CA, Bobyn JD.** The influence of stem size and extent of porous coating on femoral bone resorption after primary cementless hip arthroplasty. Clin Orthop Relat Res. 1988(231):7-28. Epub 1988/06/01.
186. **Zweymuller KA, Lintner FK, Semlitsch MF.** Biologic fixation of a press-fit titanium hip joint endoprosthesis. Clin Orthop Relat Res. 1988(235):195-206. Epub 1988/10/01.
187. **Trebse R, Milosev I, Kovac S, Mikek M, Pisot V.** Poor results from the isoelastic total hip replacement: 14-17-year follow-up of 149 cementless prostheses. Acta Orthop. 2005;76(2):169-76. Epub 2005/08/16.
188. **Glassman AH, Crowninshield RD, Schenck R, Herberts P.** A low stiffness composite biologically fixed prosthesis. Clin Orthop Relat Res. 2001(393):128-36. Epub 2002/01/05.
189. **Karrholm J, Anderberg C, Snorrason F, Thanner J, Langeland N, Malchau H, et al.** Evaluation of a femoral stem with reduced stiffness. A randomized study with use of radiostereometry and bone densitometry. J Bone Joint Surg Am. 2002;84-A(9):1651-8. Epub 2002/09/05.

190. Thien TM, Thanner J, Karrholm J. Fixation and bone remodeling around a low-modulus stem seven-year follow-up of a randomized study with use of radiostereometry and dual-energy x-ray absorptiometer. J Arthroplasty. 2012;27(1):134-42 e1. Epub 2011/05/10.

191. Homsy CA, Cain TE, Kessler FB, Anderson MS, King JW. Porous implant systems for prosthesis stabilization. Clin Orthop Relat Res. 1972;89:220-35. Epub 1972/01/01.

192. Homsy CA. Soft porous PTFE-composite alloplasts: tissue-bonding characteristics. Journal of endourology / Endourological Society. 2000;14(1):25-32. Epub 2000/03/29.

193. Keet GG, Runne WC. The Anaform endoprosthesis: a proplast-coated femoral endoprosthesis. Orthopedics. 1989;12(9):1185-90. Epub 1989/09/01.

194. Boden H, Adolphson P, Oberg M. Unstable versus stable uncemented femoral stems: a radiological study of periprosthetic bone changes in two types of uncemented stems with different concepts of fixation. Arch Orthop Trauma Surg. 2004;124(6):382-92. Epub 2004/04/28.

195. Maathuis PG, Visser JD. High failure rate of soft-interface stem coating for fixation of femoral endoprostheses. J Arthroplasty. 1996;11(5):548-52. Epub 1996/08/01.

196. Morrey BF, Adams RA, Kessler M. A conservative femoral replacement for total hip arthroplasty: A PROSPECTIVE STUDY. J Bone Joint Surg Br. 2000;82-B(7):952-8.

197. Chen H-H, Morrey BF, An K-N, Luo Z-P. Bone Remodeling Characteristics of a Short-Stemmed Total Hip Replacement. The Journal of Arthroplasty. 2009;24(6):945-50.

198. Lazarinis S, Mattsson P, Milbrink J, Mallmin H, Hailer NP. A prospective cohort study on the short collum femoris-preserving (CFP) stem using RSA and DXA. Primary stability but no prevention of proximal bone loss in 27 patients followed for 2 years. Acta Orthop. 2013;84(1):32-9. Epub 2013/01/25.

199. Schmidt R, Gollwitzer S, Nowak TE, Nowak M, Haberle L, Kress A, et al. [Periprosthetic femoral bone reaction after total hip arthroplasty with preservation of the collum femoris : CT-assisted osteodensitometry 1 and 3 years postoperatively]. Der Orthopade. 2011;40(7):591-8. Epub 2011/03/29. Periprothetische femorale Knochenreaktion nach schenkelhalserhaltender Huftendoprothetik : CT-gestutzte Osteodensitometrie 1 und 3 Jahre postoperativ.

200. Kress AM, Schmidt R, Nowak TE, Nowak M, Haeberle L, Forst R, et al. Stress-related femoral cortical and cancellous bone density loss after collum femoris preserving uncemented total hip arthroplasty: a prospective 7-year follow-up with quantitative computed tomography. Arch Orthop Trauma Surg. 2012;132(8):1111-9. Epub 2012/05/25.

201. Gotze C, Ehrenbrink J, Ehrenbrink H. [Is there a bone-preserving bone remodelling in short-stem prosthesis? DEXA analysis with the Nanos total hip arthroplasty]. Zeitschrift fur Orthopadie und Unfallchirurgie. 2010;148(4):398-405. Epub 2010/08/18. Bleibt der Krafteinfluss der Kurzschaftprothese auf den methaphysaren proximalen Femur begrenzt? Osteodensitometrische Analysen der NANOS-Schaftendoprothese.

202. Logroscino G, Ciriello V, D'Antonio E, De Tullio V, Piciocco P, Magliocchetti Lombi G, et al. Bone integration of new stemless hip implants (proxima vs. nanos). A DXA study: preliminary results. Int J Immunopathol Pharmacol. 2011;24(1 Suppl 2):113-6. Epub 2011/10/01.

203. Lerch M, Kurtz A, Stukenborg-Colsman C, Nolte I, Weigel N, Bouguecha A, et al. Bone remodeling after total hip arthroplasty with a short stemmed metaphyseal loading implant: Finite element analysis validated by a prospective dexa investigation. J Orthop Res. 2012. Epub 2012/04/20.

204. Field RE, Cronin MD, Singh PJ, Burtenshaw C, Rushton N. Bone remodeling around the Cambridge cup: A DEXA study of 50 hips over 2 years. acta orthopaedica. 2006;77(5):726-32.

205. Laursen MB, Nielsen PT, Soballe K. Bone remodelling around HA-coated acetabular cups : a DEXA study with a 3-year follow-up in a randomised trial. Int Orthop. 2007;31(2):199-204. Epub 2006/06/09.

206. Kim YH, Yoon SH, Kim JS. Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement: alumina-on-alumina versus alumina-on-polyethylene articulation. J Bone Joint Surg Br. 2007;89(2):174-9. Epub 2007/02/27.

207. Wilkinson JM, Eagleton AC, Stockley I, Peel NF, Hamer AJ, Eastell R. Effect of pamidronate on bone turnover and implant migration after total hip arthroplasty: a randomized trial. J Orthop Res. 2005;23(1):1-8. Epub 2004/12/21.

208. Wilkinson JM, Stockley I, Peel NF, Hamer AJ, Elson RA, Barrington NA, et al. Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial. J Bone Miner Res. 2001;16(3):556-64. Epub 2001/03/30.

209. Shetty N, Hamer AJ, Stockley I, Eastell R, Willkinson JM. Clinical and radiological outcome of total hip replacement five years after pamidronate therapy. A trial extension. J Bone Joint Surg Br. 2006;88(10):1309-15. Epub 2006/10/03.

210. Scott DF, Woltz JN, Smith RR. Effect of zoledronic acid on reducing femoral bone mineral density loss following total hip arthroplasty: preliminary results of a prospective randomized trial. J Arthroplasty. 2013;28(4):671-5. Epub 2012/11/13.

211. Peter B, Gauthier O, Laib S, Bujoli B, Guicheux J, Janvier P, et al. Local delivery of bisphosphonate from coated orthopedic implants increases implants mechanical stability in osteoporotic rats. Journal of biomedical materials research Part A. 2006;76(1):133-43. Epub 2005/10/29.

212. Tanzer M, Karabasz D, Krygier JJ, Cohen R, Bobyn JD. The Otto Aufranc Award: bone augmentation around and within porous implants by local bisphosphonate elution. Clin Orthop Relat Res. 2005;441:30-9. Epub 2005/12/07.

213. Thillemann TM, Pedersen AB, Mehnert F, Johnsen SP, Soballe K. Postoperative use of bisphosphonates and risk of revision after primary total hip arthroplasty: a nationwide population-based study. Bone. 2010;46(4):946-51. Epub 2010/01/28.

214. Rizzoli R, Akesson K, Bouxsein M, Kanis JA, Napoli N, Papapoulos S, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. Osteoporos Int. 2011;22(2):373-90. Epub 2010/11/19.

215. Isaacs JD, Shidiak L, Harris IA, Szomor ZL. Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. Clin Orthop Relat Res. 2010;468(12):3384-92. Epub 2010/09/03.

216. Seraphim A, Al-Hadithy N, Mordecai SC, Al-Nammari S. Do bisphosphonates cause femoral insufficiency fractures? J Orthop Traumatol. 2012;13(4):171-7. Epub 2012/08/02.

217. Albrektsson T, Albrektsson B. Osseointegration of bone implants. A review of an alternative mode of fixation. Acta Orthop Scand. 1987;58(5):567-77. Epub 1987/10/01.

218. Emerson RH, Jr., Head WC, Higgins LL. Clinical and radiographic analysis of the Mallory-Head femoral component in revision total hip arthroplasty. A minimum 8.8-year and average eleven-year follow-up study. J Bone Joint Surg Am. 2003;85-A(10):1921-6. Epub 2003/10/18.

219. Garellick G, Herberts P, Malchau H. The value of clinical data scoring systems: are traditional hip scoring systems adequate to use in evaluation after total hip surgery? J Arthroplasty. 1999;14(8):1024-9. Epub 1999/12/30.

220. Arabmotlagh M, Hennigs T, Warzecha J, Rittmeister M. Bone strength influences periprosthetic bone loss after hip arthroplasty. Clin Orthop Relat Res. 2005;440:178-83. Epub 2005/10/22.

221. Braun A, Sabah A. [Two-year results of a modular short hip stem prosthesis--a prospective study]. Zeitschrift fur Orthopadie und Unfallchirurgie. 2009;147(6):700-6. Epub 2010/02/26. Zwei-Jahres-Ergebnisse einer modularen Kurzschaft-Huftendoprothese--eine prospektive Studie.

222. Nieuwenhuijse MJ, Valstar ER, Nelissen RG. 5-year clinical and radiostereometric analysis (RSA) follow-up of 39 CUT femoral neck total hip prostheses in young osteoarthritis patients. Acta Orthop. 2012;83(4):334-41. Epub 2012/08/14.

223. Wolf O, Mattsson P, Milbrink J, Larsson S, Mallmin H. Periprosthetic bone mineral density and fixation of the uncemented CLS stem related to different weight bearing regimes: A randomized study using DXA and RSA in 38 patients followed for 5 years. Acta Orthop. 2010;81(3):286-91. Epub 2010/05/08.

224. Kim Y-H, Kim J-S, Park J-W, Joo J-H. Total hip replacement with a short metaphyseal-fitting anatomical cementless femoral component in patients aged 70 years or older. J Bone Joint Surg Br. 2011;93-B(5):587-92.

225. Kim YH, Oh JH. A comparison of a conventional versus a short, anatomical metaphyseal-fitting cementless femoral stem in the treatment of patients with a fracture of the femoral neck. J Bone Joint Surg Br. 2012;94(6):774-81. Epub 2012/05/26.

226. Huiskes R. Finite element analysis of acetabular reconstruction. Noncemented threaded cups. Acta Orthop Scand. 1987;58(6):620-5. Epub 1987/12/01.

227. Widmer KH, Zurfluh B, Morscher EW. Load transfer and fixation mode of press-fit acetabular sockets. J Arthroplasty. 2002;17(7):926-35. Epub 2002/10/11.

228. Morscher EW, Widmer KH, Bereiter H, Elke R, Schenk R. [Cementless socket fixation based on the "press-fit" concept in total hip joint arthroplasty]. Acta chirurgiae orthopaedicae et traumatologiae Cechoslovaca. 2002;69(1):8-15. Epub 2002/04/16. Zementfrei pfannenverankerung nach dem "Press-Fit-Konzept" bei der Totalprothesen-Arthroplastik der Hufte.

229. Hamilton WG, Hopper RH, Jr., Ginn SD, Hammell NP, Engh CA, Jr., Engh CA. The effect of total hip arthroplasty cup design on polyethylene wear rate. J Arthroplasty. 2005;20(7 Suppl 3):63-72. Epub 2005/10/11.

230. Sakalkale DP, Sharkey PF, Eng K, Hozack WJ, Rothman RH. Effect of femoral component offset on polyethylene wear in total hip arthroplasty. Clin Orthop Relat Res. 2001(388):125-34. Epub 2001/07/14.

231. Nygaard M, Zerahn B, Bruce C, Soballe K, Borgwardt A. Early periprosthetic femoral bone remodelling using different bearing material combinations in total hip arthroplasties: a prospective randomised study. European cells & materials. 2004;8:65-72; discussion -3. Epub 2005/01/14.

232. Albanese CV, Rendine M, De Palma F, Impagliazzo A, Falez F, Postacchini F, et al. Bone remodelling in THA: A comparative DXA scan study between conventional implants and a new stemless femoral component. A preliminary report. Hip Int. 2006;16 Suppl 3:9-15. Epub 2006/01/01.

233. Endo M, Tipper JL, Barton DC, Stone MH, Ingham E, Fisher J. Comparison of wear, wear debris and functional biological activity of moderately crosslinked and non-crosslinked polyethylenes in hip prostheses. Proceedings of the Institution of Mechanical Engineers Part H, Journal of engineering in medicine. 2002;216(2):111-22. Epub 2002/05/23.

234. Ries MD, Scott ML, Jani S. Relationship between gravimetric wear and particle generation in hip simulators: conventional compared with crosslinked polyethylene. J Bone Joint Surg Am. 2001;83-A Suppl 2 Pt 2:116-22. Epub 2001/11/20.