Revision hip arthroplasty using impacted allograft bone and cement. Studies on prosthetic stability and outcome.

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Contents

List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

Paper I

First-time revision using impacted morselized allograft bone with a cemented Exeter stem: radiostereometric analysis of stem migration over nine years.
Zampelis V, Ornstein E, Franzen H, Atroshi I.
J Bone Joint Surg Br. 2011 Jun; 93(6): 746-50.

Paper II

The effect of a biphasic injectable bone substitute on the interface strength in a rabbit knee prosthesis model.
Zampelis V, Tägil M, Lidgren L, Isaksson H, Atroshi I, Wang J S.
J Orthop Surg Res. 2013 Jul 31; 8-25.

Paper III

A simple visual analog scale for pain is as responsive as the WOMAC, the SF-36, and the EQ-5D in measuring outcomes of revision hip arthroplasty.
Zampelis V, Ornstein E, Franzen H, Atroshi I.
Acta Orthop. 2014 Apr; 85(2): 128-32.

Paper IV

Decreased migration with locally administered bisphosphonate in hip cup revisions using the bone impaction technique. A randomized, placebo-controlled study evaluated with radiostereometric analysis and dual-energy X-ray absorptiometry with a 2-year follow-up.
Zampelis V, Belfrage O, Tägil M, Sundberg M, Flivik G.
Submitted.

Abbreviations

BMC	Bone Mineral Content (g)
BMI	Body Mass Index (kg/m^2)
BMD	Bone Mineral Density (g/cm^2)
BV/TV	Bone Volume/Total Volume
CI	Confidence Interval
CN	Condition Number
DEXA	Dual-Energy X-ray Absorptiometry
EQ-5D	European Quality of Life (EuroQol) – 5 Dimensions
HA	Hydroxyapatite
IBG	Impaction Bone Grafting
OA	Osteoarthritis
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measures
ROI	Region of Interest
RSA	Radiostereometric Analysis
SD	Standard Deviation
SF-36	Short Form (36) Health Survey
THA	Total Hip Arthroplasty
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Definitions

Adaptive remodeling – Dynamic changes in bone mineral content due to different loading conditions over time.

Allograft bone – Bone graft harvested from an individual other than the recipient.

Aseptic loosening – Mechanical loosening of a prosthesis without signs of infection.

Autograft bone – Bone graft obtained from the individual receiving the graft.

Bone graft – Chips of bone produced from autograft or allograft using a bone mill or a rongeour. Used in surgical procedures that replace missing bone in order to repair bone defects.

Bone loss – Diminishing bone mass because of osteolysis or bone resorption.

Bone remodeling – Adaptive changes in bone architecture.

Bone resorption – The process by which osteoclasts break down bone and release the minerals, resulting in a transfer of calcium from bone fluid to the blood, which in turn results in a reduction in bone mass.

Hydroxyapatite – Calcium phosphate mineral; the principal stoichiometric version of the inorganic constituent of bone.

Micromotion – Small movements between a prosthetic component and the surrounding bone.

Migration – Gradual micromotion over time; the prosthesis moves from its original position to a new resting position.

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

Osteolysis – Localized area of active bone dissolution or resorption.

Prosthesis – An artificial device that replaces the function of a missing body part.

Proximal migration – Cranial migration of the prosthetic component.

Radiolucent lines – Linear radiolucencies parallel to the implant contour without densification.

Rigid body – In RSA, the number of markers forming a segment corresponding to either part of the body or an object of interest.

Revision – Reoperation with extraction of all or part(s) of the prosthetic implant.

Stress shielding – Reduction in bone density as a result of reduction of physiological stress from the bone by an implant. This is because Wolff's law states that bone in a healthy person will remodel in response to the loads it is placed under. If the loading on a bone decreases, the bone will therefore become less dense and weaker because there is no stimulus for continued remodeling, which is required to maintain bone mass.

Wear – Removal of material from implants and other materials.

Introduction

In the 1960s Sir John Charley introduced the total hip arthroplasty (THA), one of the most successful orthopedic surgical interventions (Charnley 1961). Few medical interventions have had similar impact on pain and patient autonomy. Initially, the indications for THA were largely restricted to either elderly or disabled people. Nowadays, the results of a THA with regard to reducing pain and improving function in osteoarthritic patients—as well as in patients with different hip disorders and injuries—are generally very good. The intervention has therefore been called "the operation of the century" (Learmonth et al. 2007).

Today, the most common reason for performing THA is primary osteoarthritis. In an ageing population with higher demands on physical activity, treatment of osteoarthritis with THA would be expected to increase (Kurtz et al. 2007, Skytta et al. 2011, Nemes et al. 2014). Patients less than 65 years of age are forecast to represent much (> 50%) of the anticipated demand for primary and revision total joint replacement in the United States between 2010 and 2030 (Kurtz et al. 2009).

As the number of primary THAs keeps on increasing, approximately 10% of the patients will require reoperations during their lifetime. In Sweden, the number of hip revisions between 2011 and 2014 was just below 2,000, accounting for 9.9% of all reoperation- and primary arthroplasties (Garellick 2014). In the USA, the number of hip revisions is expected to increase by 137% between the years 2005 and 2030 (Kurtz et al. 2007).

In Sweden, the most common cause of both first-time revision and multiple-time revisions is aseptic loosening, accounting for 44% of revision operations, also including osteolysis (Garellick 2014) .

Although the pathological basis of aseptic loosening is complex, different possible etiologies have been proposed, such as early instability of the prostheses due to insufficient initial fixation and also wear-induced osteolysis. In general, the initial response is a localized inflammatory response, which is characterized by the formation of fibrous tissue around the cement or the prosthesis. This layer of fibrous tissue has negligible stiffness and strength, and does not provide a stable surrounding for the prosthesis—resulting in prosthetic movement known as micromotion. This process of prosthetic micromotion leads to aseptic loosening, and once started, it is continuous and contributes to bone resorption around the implant (osteolysis), resulting in more prosthetic loosening (Figure 1).
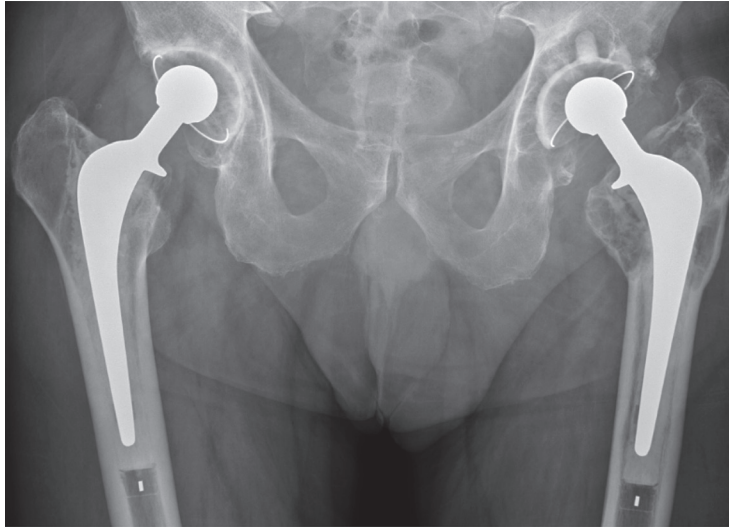
Figure 1. Patient with bilateral hip prostheses with radiographic and clinical signs of prosthetic loosening with associated osteolysis around the left cup and stem component. Signs of polyethylene wear are evident in both acetabular cups.

Prosthetic design and surgical technique

The process of achieving and maintaining prosthetic fixation is influenced by various factors that, in simple terms, can be related to the patient (bone quality and related bone defects), to the surgical technique, and to the implant used. Assuming that we cannot change the patient-related factors, we must focus on factors related to the implants and the choice of surgical technique in order to address the problem of bone resorption (osteolysis) and associated loosening.

In hip arthroplasty, new prosthetic designs, materials, and procedures are continuously being introduced with the aim of achieving better prosthetic fixation and prevention of loosening. Despite this, it appears that there is no strict obvious logical relationship between implant design and performance. As an example, the two most commonly used and well performing femoral components in Sweden are fundamentally different (Garellick 2014). The Lubinus SP II femoral component has a curved cobalt-chrome alloy stem with a matte surface and a collar. The Exeter femoral component features a straight, double-tapered, polished stainless steel stem and no collar. The former implant is intended to function through stable fixation with cement. The latter is designed to—or rather, has been found to—subside within the cement mantle, obviously without any detrimental effect on the clinical function.

This may give the false impression that design does not matter, but on the contrary, design and manufacturing do matter.

There are numerous historical examples of newly introduced implants that have failed to meet expectations in terms of performance and survival. The Christiansen hip prosthesis in the 1970s and the Boneloc cement in the 1990s have unfortunately contributed to a large number of "unnecessary" revision procedures. Today, most of the commonly used implants are suitable for most of our patients, but still, we continue to try and improve methods, implants, and results. The many implant failures throughout orthopedic history highlight the importance of stepwise introduction of new implants (Malchau 1995, Nelissen et al. 2011). New implants should preferably be introduced through large-scale observational studies, such as in the Swedish Hip Arthroplasty Register, the results of which can be directly extrapolated to improve clinical practice (Malchau et al. 2015).

Careful preoperative planning is a prerequisite for successful revision surgery. The principal aims in revision hip arthroplasty are to ensure the support of the host bone, to secure implant fixation, and to restore the center of the hip and the joint kinematics. The type and severity of host bone loss determine the method of reconstruction. Careful preoperative planning improves effectiveness during surgery, and helps in the choice of different alternatives for reconstruction. Thus, the optimal surgical approach for restoring femoral and acetabular bone stock in revision hip arthroplasty varies considerably in different settings. Nonetheless, restoration of the bone stock is essential—not only for better prosthetic survival, functional improvement, and pain reduction, but also to provide a better starting point for any subsequent revision.

Impaction bone grafting (IBG) is an attractive biological reconstruction method in revision hip surgery; it was introduced by Slooff and co-workers in 1984 (Slooff et al. 1984). These authors reported their initial experience with acetabular impaction bone grafting in cemented primary and revision hip arthroplasty, in the presence of acetabular protrusion and deficient bone stock. The method was later modified for femoral revision in the early 1990s by the Exeter group (Gie et al. 1993). Long-term follow-up data have shown excellent prosthetic survival, varying between 94% and 98% beyond 10 years, with the use of a cemented femoral component with IBG (Ornstein et al. 2009, Lamberton et al. 2011). In addition, good prosthetic survival of between 75% and 88% beyond 20 years has been shown regarding acetabular revision with IBG (Schreurs et al. 2009, van Egmond et al. 2011). Nevertheless, concerns have been raised that IBG in acetabular revision with severe bone defects may give poorer results (72% at 20 years) than previously reported (van Haaren et al. 2007).

Impaction bone grafting and bisphosphonates

Autologous bone is considered to be the gold standard in bone grafting. It is usually not a feasible option for revision surgery, due to the large amount needed in revision hip arthroplasty. The current standard is therefore allograft bone, most commonly frozen femoral heads collected from primary arthroplasties and stored in a bone bank. The allograft is morselized into bone chips at the revision surgery (Board et al. 2006) and impacted into the femoral canal and/or acetabular cavity, reconstructing all secondary bone stock defects. Thereafter, the prosthesis is cemented in place, creating a three-layer composite consisting of implant, cement, and graft.

Histological examination of specimens obtained from studies conducted on humans indicate that impacted allograft bone in the acetabulum remodels almost completely into new vital bone (van der Donk et al. 2002), but to a lesser extent in the femur (Ullmark and Obrant 2002). The short-term success of revision arthroplasty with impaction grafting is related to the initial mechanical stability of the construct. However, the long-term outcome is biological and will depend on the graft incorporation and remodeling into new and vital bone, forming a lasting bond between the graft and the host. During remodeling of the graft from non-vital to vital bone, it is important that a balance between graft resorption and new bone formation is maintained to achieve stable prosthetic conditions. In normal bone remodeling, there is a coupling between bone resorption and bone formation. This may be different in situations such as implant fixation, where resorption and formation are uncoupled and the balance between these two responses is more important. If the implanted graft is resorbed too quickly, then the stability of the construct may be affected and as a consequence may result in new prosthetic loosening. Thus, manipulation of the graft to either decrease graft resorption or increase new bone formation may be important to provide a more stable construct.

Bisphosphonates are currently the major class of drugs used for the treatment of osteoporosis and other diseases characterized by increased bone resorption. Through their ability to bind to bone mineral and inhibit mature osteoclasts, bisphosphonates inhibit bone resorption (Russell et al. 2008). It could be speculated that treatment of the allograft with bisphosphonates might be a method to improve the result of impaction bone grafting technique by delaying early bone graft resorption. Resorption reduced by a bisphosphonate leaves bone formation partially undisturbed, so that a net gain in bone is achieved, providing a stable scaffold in which the allograft will remodel into new and vital bone. Nevertheless, whether delayed or decreased graft resorption results in an increase in bone density and consequently to increased prosthetic stability—secondarily reducing the risk of mechanical failure—remains unclear.

Radiographic loosening

Although there is general agreement that revision hip arthroplasty is indicated when a patient presents with a painful, loose prosthesis, it is difficult to detect early prosthetic loosening on plain radiographs. There is no consensus concerning the definition of implant "loosening". Distinctions are made between clinical and radiographic loosening. Radiographic loosening of prostheses is assessed indirectly in successive radiographs by measuring radiolucent lines around the prosthesis and differences in position of the prosthesis relative to the surrounding bone. Radiolucent lines indicate the presence of a fibrous layer, and their presence is associated with increased risk of later clinical loosening. However, these measurements are not accurate—as bony landmarks used for their evaluation are not sufficiently distinctive and are therefore difficult to measure in a reproducible manner. When the measurements are based on bony landmarks, cup migration is only detectable on conventional radiographs when it exceeds 3–4 mm and stem migration when subsidence exceeds 4 mm (Malchau et al. 1995). Thus, radiographic examination has proven to be inadequate in assessment of early mechanical loosening (Mjoberg et al. 1986).

If loosening, defined as migration, is the change in position of an implant, then the definition of migration is determined by the accuracy of the method by which it is assessed. In 1974, Selvik developed a highly accurate technique for the assessment of a three-dimensional migration, Radiostereometric analysis (RSA) (Selvik 1989). With the development of RSA, early-stage prosthetic loosening could be detected with a precision ranging between 0.15 and 0.6 mm for translations and between 0.3° and 2° for rotations (Karrholm 1989, Karrholm et al. 1997) around the three axes in an orthogonal coordinate system. This critical difference in the accuracy between radiographic assessment of the radiolucent lines and RSA would, in clinical practice, mean that many prostheses that appear to be stable on conventional radiography can show loosening when examined with the more sensitive RSA. Thus, due to the high accuracy of the RSA method, prosthetic migration can be identified long before clinical failure is evident, and therefore RSA is considered to be the gold standard technique for measurement of three-dimensional prosthetic micromotion (Carlsson et al. 1993, Biedermann et al. 1999)

Almost a decade after introduction of the RSA method, the predictive value of early prosthetic migration and the risk of subsequent revision due to loosening was evaluated (Karrholm et al. 1994, Ryd et al. 1995). The hypothesis that early migration could be used as a surrogate variable for clinically relevant loosening was confirmed in studies on primary joint arthroplasty (Karrholm et al. 1994, Ryd et al. 1995, Nieuwenhuijse et al. 2012a, Pijls et al. 2012).

However, recent studies on primary hip arthroplasty have failed to show a correlation between clinical failure and migration of the polished, collarless, and tapered Exeter stem (Nieuwenhuijse et al. 2012a, Murray et al. 2013). The upper limit and

time frame for acceptable early migration varies depending on several factors such as the type of implant, the type of fixation, and whether bone graft has been used. Nevertheless, there is no doubt that migration below the detection level of RSA is a good prognostic sign concerning the risk of later clinical loosening.

Clinical loosening

From a more practical point of view, fixation of a prosthesis may be regarded as a continuous entity ranging from stable fixation to migration, and ultimately to gross mechanical loosening. At some stage the lack of fixation may eventually give clinical symptoms, which often present as pain and reduced physical activity.

It is difficult to evaluate the results of hip surgery. There is no clear definition of expected outcomes. The preoperative health and the expectations of the patients may differ, and the state of health may change over time for reasons unrelated to the hip surgery. Thus, the patient-reported outcome is probably the most important measure to evaluate the value of a surgical procedure to measure the effect on the primary indications, namely to relieve pain and restore function.

Methods to assess a patient's perception of effect of surgery-related disability will not only expose any adverse events or failures associated with the surgery, but it will also identify whether realistic expectations discussed preoperatively have been fulfilled postoperatively. These methods must therefore be easy for patients to use, and their results must be comparable—as these truly indicate the patient's assessment of outcome.

This thesis is the result of efforts to address specific clinical questions that arise in our daily arthroplasty work. It addresses questions pertaining to aspects of fixation of hip prostheses in revision settings, to which we seek answers by means of clinical research.

Aims and hypotheses of the thesis

The general aim of this thesis was to study prosthetic fixation and patient outcome, and to assess alternatives for improvement of prosthetic fixation in hip revision.

The specific aims in each study were:
I.   To investigate with RSA the migration of the Exeter stem in relation to the long-term clinical outcome, 9 years after revision, using morselized allograft bone and cement.
II.   To investigate and compare prosthetic fixation and tissue integration with and without the use of an injectable biphasic bone substitute in an experimental primary tibia prosthesis rabbit model.
III. To compare the performance of four commonly used measures of patient-reported outcomes in revision hip arthroplasty, tools which are helpful when designing clinical studies or when choosing outcome measures for use in registries.
IV.   To investigate whether the effect of pharmacological treatment of allograft bone with a bisphosphonate reduces allograft resorption in hip revision arthroplasty.

Hypotheses of the thesis

I.   Continuous migration, although compatible with the design of the Exeter stem, would be associated with clinical signs of loosening and poor long-term survival.
II.   A biphasic bone void filler would increase tissue integration and thus achieve more stable prosthetic fixation.
III. Different patient-reported outcome measures vary in their responsiveness in patients undergoing revision arthroplasty.
IV.   An increased bone density, achieved by treating the allograft with a bisphosphonate, would lead to reduced prosthetic micromotion.

Bone grafts

Bone grafting is a surgical procedure that replaces missing bone and stimulates new bone formation. The demand for bone graft in revision hip surgery has significantly increased because of the growing number of failed total hip arthroplasties requiring not only a reoperation with a new prosthesis, but also the restoration of the peri-prosthetic bone stock, lost in the process of loosening. The long-term outcome of revision hip arthroplasty is highly dependent on reconstructing the bone loss and ensuring implant stability. Bone grafts therefore serve two functions: in the short term, mechanical support by providing instant prosthetic stability allowing immediate weight bearing; and in the long term, biological function involving restoration of bone stock by remodeling and incorporation of the non-vital bone graft to vital new bone. Even so, differences in the extent of remodeling of the impacted bone graft in the femur and the acetabulum (Ullmark and Linder 1998, Linder 2000, Ullmark and Obrant 2002, van der Donk et al. 2002) indicate the significant role of the anatomical site in which the bone graft is used.

The incorporation of any bone graft is a dynamic process that involves a common sequence of biological events: initial inflammation, revascularization of the bone, resorption of the donor bone, substitution of the graft with new host bone, and finally remodeling of the construct to provide the required mechanical and biological support to the skeleton (Goldberg and Stevenson 1993). Processes that allow this biological cascade are: osteogenesis, osteoinduction, and osteoconduction—along with the final bonding between host bone and grafting material, which is called osteointegration.

Osteogenesis means the formation of bone, which is a central biological function of all grafts and is often related to the presence of bone-forming cells within the bone graft. Osteogenesis includes the ability of the graft to provide progenitor cells with osteogenenic potential, to directly lay down new bone. *Osteoinduction* means stimulation and activation of osteoprogenitor cells from the surrounding host tissue, cells that can differentiate into osteoblasts and also lay down new bone (Goldberg 2000). Finally, *osteoconduction* is defined as the function of a bone graft to provide a three-dimensional structure that acts as a trellis for the ingrowth of host capillaries and osteoprogenitor cells (Goldberg 2000). Finally, osteointegration relates to the surface bonding between the host bone and the grafting material. Ultimately, a bone graft must provide structural support for the host bone, either as its primary function or as a result of the remodeling of the original graft under the influence of mechanical load and normal bone turnover in the environment of the host.
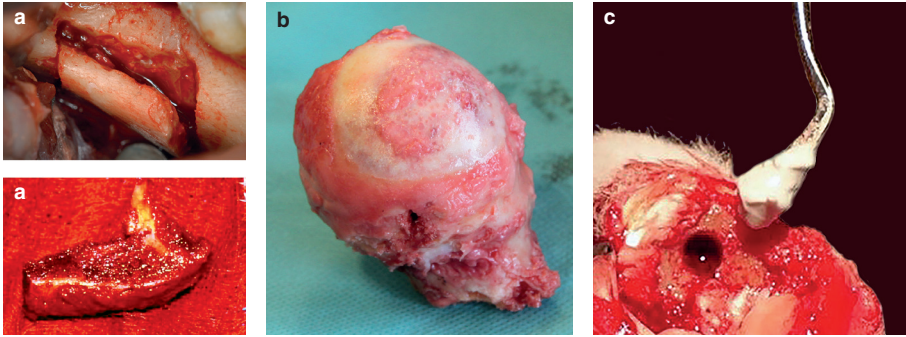
Figure 2. Types of bone grafts: autologous (a); allograft (b); synthetic (c).

Bone grafts may be autologous (bone harvested from the patient's own body, often from the iliac crest), allograft (bone transplanted from one individual; often donated by patients undergoing primary hip arthroplasty), or synthetic bone graft substitutes, all of which are biologically active—but to different degrees (Figure 2).

Autogenous bone is the most effective graft material for biological function. However, the large bone deficiencies usually present in revision hip arthroplasty have required the use of allografts. Autologous and allograft bone can be either cancellous or cortical bone grafts. Cancellous bone grafts have a greater potential to form new bone because of their large surface area compared to the more dense cortical bone.

Allografts can be used as structural or morselized grafts. Allografts are prepared in fresh-frozen or freeze-dried forms, cortical or cancellous. Fresh allografts induce an intense immunological response and are therefore no longer used clinically. In contrast, fresh-frozen allografts induce stronger immune responses than freeze-dried allografts which have weaker biological and mechanical properties due to their additional processing. The more aggressive the allograft processing is, the less intense the immunological responses and the weaker the biological and mechanical properties of the bone graft will be. Thus, fresh-frozen and freeze-dried allografts are not osteogenic and are considered to have weak, if any, osteoinductive capability compared to fresh autograft, but they are osteoconductive (Khan et al. 2005) (Table 1).

Another issue related to the use of allogenic bone is the risk of transmitting potential pathogens such as human immunodeficiency virus (HIV), hepatitis B virus, and hepatitis C virus. Tissue banks that adhere to international standards, including extensive donor screening and serological testing, minimize the transmission of disease in bone allografts.

Due to the large amount of bone graft often required to address bone stock deficiency, revision hip arthroplasty requiring impaction bone grafting is most often performed using fresh-frozen femoral heads. These are usually donated by patients undergoing primary hip arthroplasty. Following donation, the femoral head allograft

Table 1. Bone graft activity by type. The symbols –, +, ++, +++ show the extent of activity. – means no activity, and + + + means maximal activity. Table adapted from Khan et al. (2005)

Graft	Osteogenesis	Osteoinduction	Osteoconduction	Mechanical properties	Vascularized
Autograft					
Bone marrow	++	+	+/–	–	–
Cancellous	++	+	++	+	–
Cortical	+	+/–	+	++	–
Vascularized	++	+	++	++	+
Allograft					
Cancellous	–	+	++	+	–
Cortical	–	+/–	+/–	++	–
Demineralized	–	+++	++	–	–

is kept under sterile conditions in a bone bank at −80 °C. The frozen femoral head is thawed at the time of surgery and milled to the required size.

Thus, the challenges of hip revision include not only addressing bone loss and poor bone biology but also allograft maintenance, scanning, and preservation. Hence, in order to overcome this, synthetic bone graft substitute alternatives have been tried over the past decade.

The ideal bone substitute should be osteogenetic, osteoinductive, and osteo-conductive without the risk of transferring infectious diseases; readily available; manageable; biocompatible; bioresorbable; cheap; and off-the-shelf. Moreover, it should induce minimal or no fibrotic reaction, undergo remodeling, and support new bone formation. From a mechanical point of view, bone substitutes should have a stiffness similar to that of the bone being replaced, in an attempt to reduce stress shielding and give sufficient strength under cyclic loading.

Synthetic bone grafts are divided into ceramics and cements. Synthetic bone substitutes have habitually been based on calcium phosphate and/or calcium sulfate materials, which are osteoconductive and facilitate bone remodeling (Calori et al. 2011).

Most injectable bone substitutes are delivered as dry powders and a fluid, which are mixed together in the operating room—either manually or using a mixing system. After mixing, the paste-like cement is injectable for a few minutes, after which it cures through either an exothermic or an isothermal reaction.

Calcium sulfate is available as a dry powder, which is hardened by crystallization in an exothermic reaction following addition of water. Calcium sulfate is considered to be biocompatible, but the usefulness of pure calcium sulfate in the clinical setting is limited—as it is rapidly resorbed (within 6–12 weeks), failing to provide the long-term three-dimensional framework necessary to support osteoconduction (Beuerlein and McKee 2010). Thus, calcium sulfate has been criticized for its rapid resorption before the bone tissues have had time to grow into the defect. In contrast, hydroxyapatite (HA) has both good mechanical strength and resistance to resorption, and also osteoconductive properties that promote early bone ingrowth (Wang et al. 1994). Hence, incorporation of calcium sulfate into the hydroxyapatite is a way

of achieving a material with good mechanical binding properties. By combining calcium sulfate (60%), hydroxyapatite particles (40%), and a radiopaque enhancing agent (ioxenol) for visibility under fluoroscopy with water, an injectable, biphasic bone graft ceramic substitute composite is formed (Cerament; Bone Support AB, Lund, Sweden). It is made synthetically and has one slowly resorbing osteoconductive component (hydroxyapatite) and one resorbable component (calcium sulfate).

Cerament has a compressive strength comparable to that of healthy cancellous bone (Nilsson et al. 2002) and combines "cement properties" with those of a void filler. Once implanted, the calcium sulfate component gradually dissolves, creating pores in the implant, which are theoretically replaced by ingrowing bone. The new-formed bone remodels to form trabecular bone protected by the hydroxyapatite particles as a three-dimensional osteoconductive matrix. Thus, Cerament has features that are desirable in the bone remodeling process. Good clinical results have been reported related to pain reduction and bone healing quality on radiographic evaluation in distal radius fractures, vertebral fractures, tibial plateau fractures, and benign bone tumors, and also related to its use as a delivery vehicle for antibiotics (Abramo et al. 2010, Hatten and Voor 2012, Marcia et al. 2012, Nusselt et al. 2014, Kaczmarczyk et al. 2015, McNally et al. 2016). To our knowledge, no trials using Cerament as a bone substitute in hip revision have been reported, leaving this aspect open for future exploration.
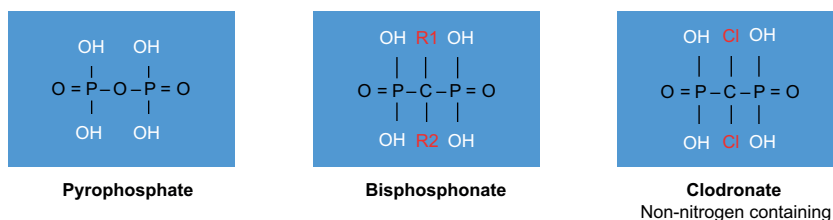
Bisphosphonates

Bisphosphonates are analogs of the natural pyrophosphate found in bone. They were first synthesized in 1865 and have been used in clinical practice since the 1960s. Pyrophosphate is the body's own "water softener"; it prevents calcification of soft tissues, inhibits the dissolution of hydroxyapatite crystals, and regulates bone mineralization.

Bisphosphonates have a high affinity for hydroxyapatite and a high avidity for calcium ions, which is the basis of the bone-targeting property of these compounds. Bisphosphonates incorporate into sites of active osteoclast-mediated bone resorption, affecting osteoclast activity. The effect on the osteoclast leads to a decrease in bone turnover and, secondly, to the inhibition of bone resorption (Russell 2006).

Bisphosphonates of medical interest are stable analogs of the naturally occurring pyrophosphate (P–O–P) found in bone, where the central oxygen atom is changed to a carbon atom with two side chains (R1 and R2) and the two original phosphate groups (Figure 3).

The P–C–P structure, unlike the P–O–P structure, is highly resistant to osteolysis. The R1 side chain is usually a hydroxyl (OH) group. The two phosphate groups, together with a hydroxyl group at the R1 position, ensure high affinity for bone mineral and act as a "bone hook". Bisphosphonates adhere to the bone mineral to such an extent that the binding is considered practically permanent, and lasts until the bone is resorbed. Once localized within bone, the R2 side chain defines the potency of the bisphosphonate and the ability of the drug to interact with specific molecular targets. Addition of an amino (nitrogen-containing) group to the R2 side chain increases the binding affinity 10 times (Leu et al. 2006) and the anti-resorptive potency by 1,000

Figure 3. The structure of pyrophosphate, bisphosphonates, and clodronate. R1 and R2 are variable side chains.

fold (Rogers et al. 2000). Potency can be increased further by modification of the primary amine to form a tertiary amine, but still leaving the hydroxyl (OH) group on the R1 side chain unchanged. The bisphosphonates containing a nitrogen atom within a heterocyclic ring are the most potent anti-resorptives.

Bisphosphonates fall into two different groups, with a mode of action resulting in either osteoclast inhibition or osteoclast death. The first group contains the least potent, non-nitrogen-containing bisphosphonates (etidronate, clodronate, and tiludronate) most closely resembling pyrophosphate, which can be incorporated into non-hydrolyzable cytotoxic analogs of ATP—causing apoptosis of the osteoclast. The second group, the nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) are not metabolized, but inhibit protein prenylation in the mevalonate pathway, which is fundamental to osteoclast formation and function (Russell 2006). This inhibition could explain why nitrogen-containing bisphosphonates are more potent regarding reduction of osteoclast activity associated with normal remodeling of bone.

Bisphosphonates are not distributed homogeneously to bone. Their binding occurs preferentially in areas of high bone turnover. Once taken up by bone, approximately one-third to two-thirds of the bisphosphonates administered become incorporated into the skeleton and the remainder is excreted in the urine (Russell et al. 2008). Bisphosphonates are retained at sites of high bone turnover during the process of remodeling, and then become buried in the skeleton and are liberated again only when the bone in which they are deposited is resorbed. Thus, the release of bisphosphonates from bone is largely dependent on remodeling and resorption (Russell et al. 2008). Bisphosphonates that are not retained in the skeleton are rapidly cleared from the circulation by renal excretion. All bisphosphonates are very poorly absorbed from the gastrointestinal tract (1–2% of the dose administered).

The total dose of bisphosphonates administered is a major determinant of their effects. The same degree of inhibition of bone resorption is accomplished whether bisphosphonates are given in small doses frequently or in larger doses but less frequently (Bauss and Russell 2004, Gasser et al. 2008).

The study in paper IV used clodronate, a non-nitrogen-containing bisphosphonate used in a previous study (Kesteris and Aspenberg 2006). Both R-side chains consist of chloride atoms, giving a small molecule with a relatively low bone affinity. Clodronate can be administered orally, as an intravenous infusion (Kanis and McCloskey 1997), or locally (Aspenberg and Astrand 2002)—as done in this study.

Classification of bone stock loss

Preoperative assessment of bone loss is important. Several systems have been used to classify the severity of bone loss in THA. Acurate preoperative identification of the structural integrity of the bone of interest, as preoperative planning is essential to ensure the available options for fixation, appropriate equipment and prostheses available.

The classifications used in papers I and IV were the Gustilo and Pasternak classification regarding femoral bone loss and the Paprosky classification regarding acetabular bone loss.

The Gustilo and Pasternak classification of proximal femoral defects is used to assess the amount of bone loss and define the morphology of the remaining proximal femoral bone stock (Table 2) (Gustilo and Pasternak 1988).

Preoperative bone loss in the acetabulum, seen on conventional radiographs, was classified according to Paprosky et al. (Paprosky et al. 1994). The Paprosky classification makes use of radiographs taken before the revision surgery to classify defects according to the presence or absence of intact acetabular walls, and the ability of the anterior and posterior columns to support an implant (Table 3).

Table 2. Femoral bone stock deficiency, types I to IV, according to Gustilo and Pasternak. Adapted from Gustilo and Pasternak (1998).

Type	Description
I	Bone loss with minimal endosteal or inner cortical bone loss, i.e loosening of the cement-metal-bone interface or broken stem.
II	Proximal femoral canal enlargement with cortical thinning of 50% or more and sometimes there is a lateral wall defect with an intact circumferential wall. The most important difference with Type I is at Type II there is loss of almost all trabecular bone.
III	Posterior-medial wall defects involve the lesser trochanter, indicating instability.
IV	Total circumferential loss of bone at varying distances below the lesser trochanter.

Table 3. Acetabular bone stock deficiency types I to III according to Paprosky. Adapted from Paprosky and Perona 1994

Classification	Tear drop	Hip center	Köhler line	Ischium	Bone loss
Type I	Intact	No migration	Intact	Intact	Mild (> 50% cancellous)
Type II					
II-A	Intact	Mild migration (< 2 cm superomedial)	Intact	Intact	Moderate (< 50% cancellous)
II-B	Intact	Moderate migration (< 2 cm superolateral)	Intact	Intact	Moderate (< 50% cancellous)
II-C	Moderate lysis	Mild migration (< 2 cm medial)	Disrupted	Intact	Moderate (< 50% cancellous)
Type III					
III-A	Moderate lysis	Severe migration (> 2 cm superolateral)	Intact	Moderate lysis	Severe (10- to 2-o'clock loss, 40–70% sclerotic)
III-B	Severe lysis	Severe migration (> 2 cm superomedial)	Disrupted	Severe lysis	Severe (9- to 5-o'clock loss, 30% sclerotic)

Materials and methods

Clinical studies

All three clinical studies were prospective, single-center studies. The patients in the studies were osteoarthritic patients with aseptic prosthetic loosening after primary arthroplasty, undergoing first-time hip revision surgery performed with impaction bone grafting and cemented Exeter prosthesis.

Paper I: First-time revision using impacted morselized allograft bone with a cemented Exeter stem: radiostereometric analysis of stem migration over nine years.
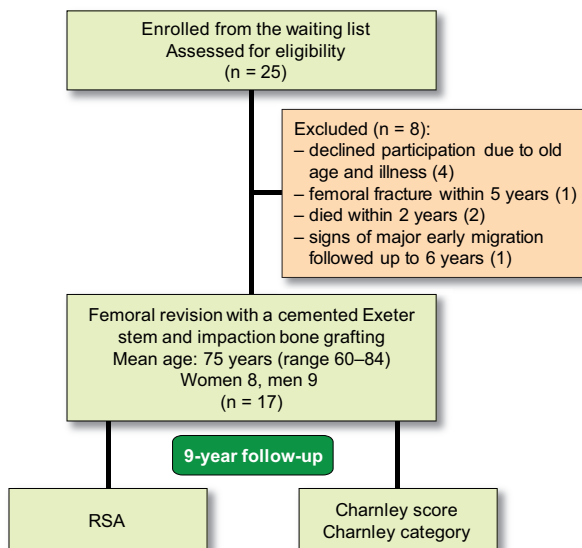
This was a prospective cohort study carried out at one orthopedics department. We studied the long-term migration pattern of the cemented Exeter stem in 17 patients who were revised between January 1994 and December 1995 with impaction of morselized allograft bone and a cemented Exeter prosthesis. The 9-year follow-up included annual RSA examinations, and clinical assessments with the Charnley score and category (Tables 4 and 5, Figure 4).

Table 4. Patient characteristics in the clinical studies (papers I, III, and IV)

Paper:	I	III	IV
Date of operation	January 1994 to December 1995	March 2006 to February 2008	February 2008 to March 2012
Follow-up in years	9	2	2
Indication for revision	Aseptic loosening	Aseptic loosening	Aseptic loosening
Number of patients for final follow-up	17	45	18
Age at revision, mean (range)	75 (60–84)	74 (60–89)	72 (56–86)
Women / men	8 / 9	20 / 25	7 / 11

Table 5. Methods used in the clinical studies (papers I, III, and IV)

Paper:	I	III	IV
Impaction bone grafting (IBG)	x	x	x
Charnley score and category	x		
WOMAC		x	
SF-36		x	
EQ-5D		x	
Pain VAS		x	
Patient satisfaction		x	
Radiostereometric analysis (RSA)	x		x
Dual X-ray absorptiometry (DEXA)			x

Figure 4. Layout of paper I.

Paper III: A simple visual analog scale for pain is as responsive as the WOMAC, the SF-36, and the EQ-5D in measuring outcomes of revision hip arthroplasty.

This was a prospective cohort study carried out at one orthopedics department. The study compared the performance of the WOMAC, the SF-36, the EQ-5D, and a visual analog scale (VAS) for pain, which were completed by patients at baseline and 2 years after revision hip arthroplasty performed with impaction bone grafting (Tables 4 and 5, Figure 5).
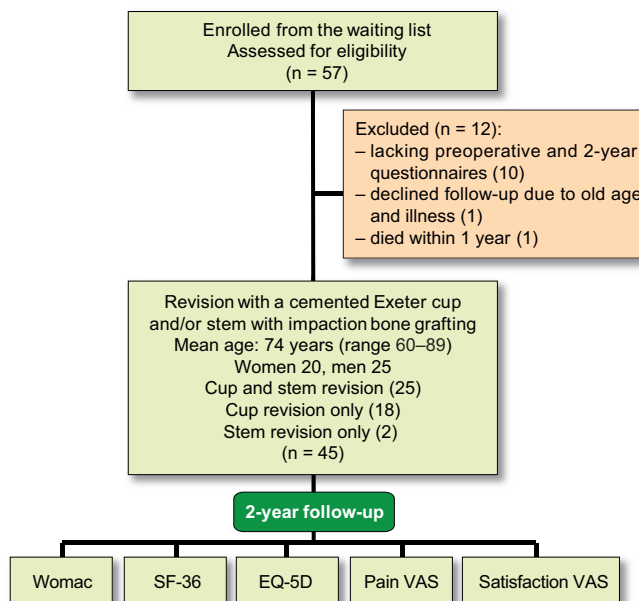
Figure 5. Layout of paper III.

24

Paper IV: Decreased migration with locally administered bisphosphonate in hip cup revisions using the bone impaction technique. A randomized, placebo-controlled study evaluated with radiostereometric analysis and dual-energy X-ray absorptiometry with a 2-year follow-up.

The study was designed as a single-center, randomized, double-blind, placebo-controlled prospective study. The inclusion criteria were that the patient should be aged between 55 and 85 years with aseptic loosening of the acetabular prosthetic component following a primary total hip arthroplasty (THA) and first-time revision (replacement of the cup component) with a follow-up of 2 years. Patients included were taken consecutively from the waiting list of the study department and were operated on between February 2008 and March 2012. The study included only patients who were revised with impaction of morselized allograft bone and a cemented Exeter cup prosthesis. The patients were followed for 2 years with RSA, and with dual-energy X-ray absorptiometry (DEXA) for one year (Tables 4 and 5, Figures 6a and 6b).
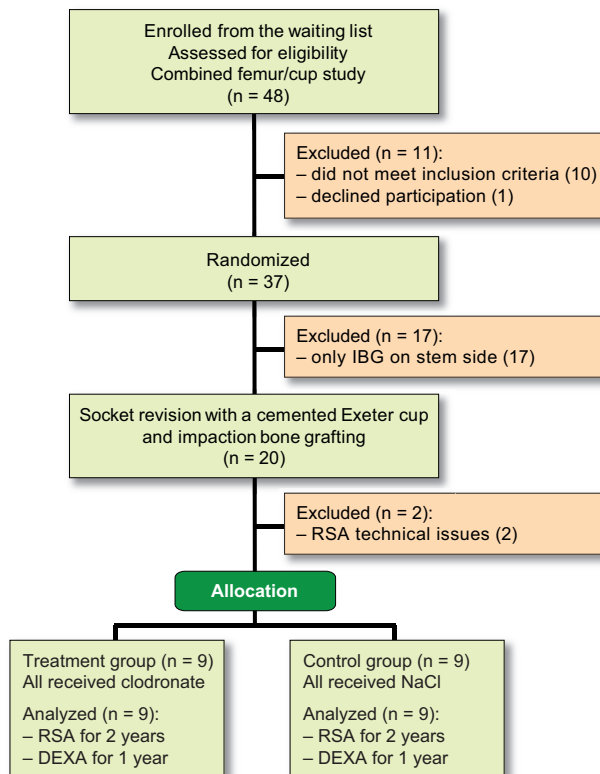
Figure 6a. Layout of in paper IV.

	Clodronate (n = 9)	Control (n = 9)
Age (range)	72 (64–80)	72 (55–85)
Women / men	2 / 7	5 / 4
Body Mass Index	27.4 (22–31)	27.4 (22–35)
Paprosky 2A / 2B / 2C	6 / 1 / 2	2 / 5 / 2
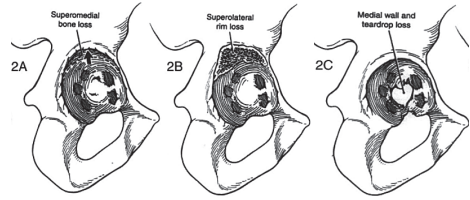
Figure 6b. Patient demographics in paper IV and illustration of Paprosky classification.

Implants

Figure 7. Implants used in study I, III, and IV: (a) universal Exeter stem, (b) Contemporary Exeter cup, (c) Exeter X3 RimFit cup.

Surgical technique

All revisions were performed by experienced surgeons, using a posterolateral approach. The Exeter stem and/or cup components (Stryker International, London, UK) were inserted in all three clinical studies, in conjunction with the allograft impaction technique as described by Gie (Gie et al. 1993) using the Exeter X-Change Revision Instrument System (Stryker, Kalamazoo, MI, USA). Allograft, in the form of fresh-frozen femoral heads donated by patients undergoing primary hip arthroplasty, was used to restore the bone stock deficiencies. Following donation, the femoral head allografts were kept under sterile conditions in a bone bank at −80 °C until they were used. The frozen femoral heads were thawed, in plain saline (at 50–60 °C) in papers I and III and in saline containing 1 g gentamycin in paper IV, for 20 min at the time of surgery. Thereafter, cartilage and sclerotic bone were removed and the femoral heads were milled to produce bone chips of 3–8 mm (Figure 8a).
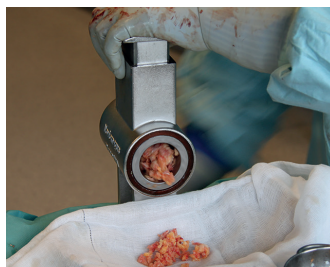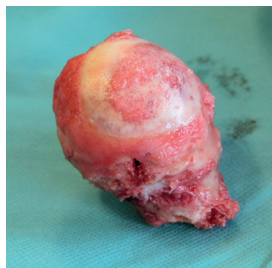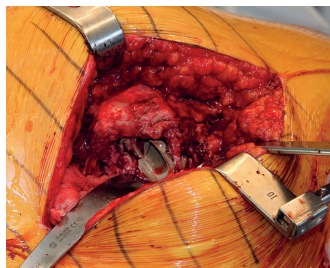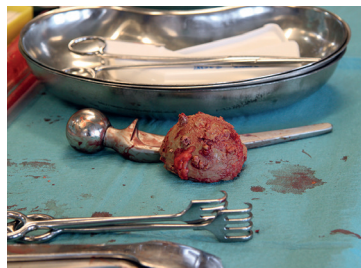
Figure 8a. Removal of the loose hip prosthesis and preparation of the allograft bone.

In paper IV, for allocation of the patients, envelopes were prepared containing the text "clodronate" or "saline" in equal numbers, together with mixing instructions. The envelopes were then closed, randomly mixed, and numbered. The closed envelopes were opened during the preoperative preparations by the assisting nurse, who accordingly poured either clodronate or saline into a cup for later mixing with the morselized graft. The scrub nurse, the surgeon, and the patient were all blind as to the patient's group allocation. Once the bone chips were produced, they were placed and soaked for at least 10 min in a metal bowl containing 510 mL of experimental solution; i.e. 500 mL of plain saline (NaCl, 9 mg/mL) and either 10 mL of plain saline (control group) or 10 mL of 60 mg/mL clodronate (treatment group). Finally, in all three studies allograft bone chips were rinsed and compressed in cotton cloth before implantation (Figure 8b).
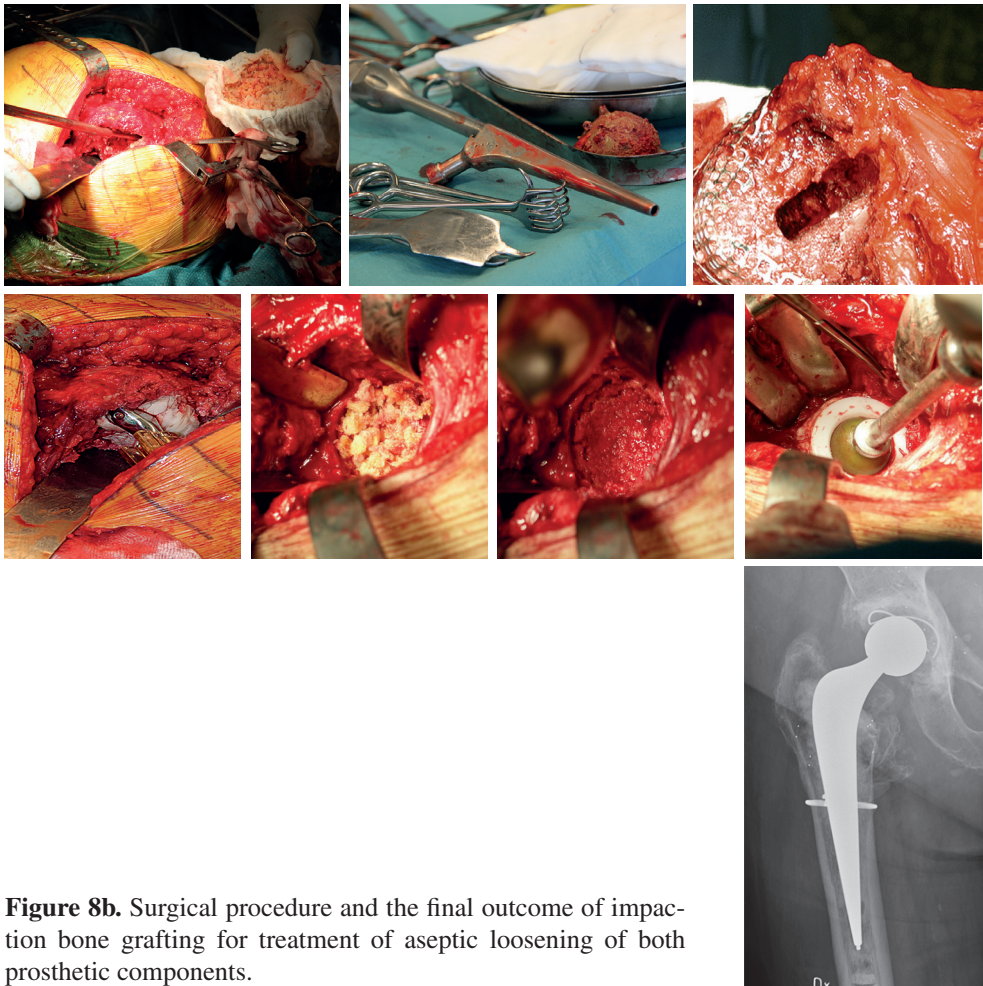
Figure 8b. Surgical procedure and the final outcome of impaction bone grafting for treatment of aseptic loosening of both prosthetic components.

Radiosterometric analysis (RSA)

RSA is a highly accurate technique for the assessment of three-dimensional migration of joint prostheses. It was developed in Lund and introduced by Göran Selvik (Selvik 1974). RSA quantifies the three-dimensional motion of an implant relative to the host bone and relative to the cement mantle. Two RSA set-ups are available; the marker-based RSA used in this thesis and model-based RSA. Both RSA methods require intraoperative insertion of radio-dense spherical tantalum markers in the skeleton, which serve as well-defined landmarks. The tantalum markers are inserted into bone with a special insertion instrument (Figure 9). These markers, which are biocompatible and well-tolerated by the body, have diameters of 0.5, 0.8, or 1.0 mm and are readily observed as distinct points on the radiograph. Due to their small and spherical shape, their projection will not be influenced by changes in patient position or X-ray focus position. The position of these markers can therefore be measured with great accuracy.

At least three non-collinear markers should be inserted within each bony structure studied, although the use of 6–9 well-scattered bone markers is recommended (Valstar et al. 2005) (Figure 9). The use of additional markers (more than 3) will increase the accuracy of the procedure. Additionally, the precision of the RSA measurements will increase when the markers are appropriately scattered in the bone surrounding the implant. Thus, the fundamental principle of RSA is the presence of tantalum markers in the bone surrounding the implant; any change in prosthesis position and orientation is calculated relative to this static reference coordinate system.
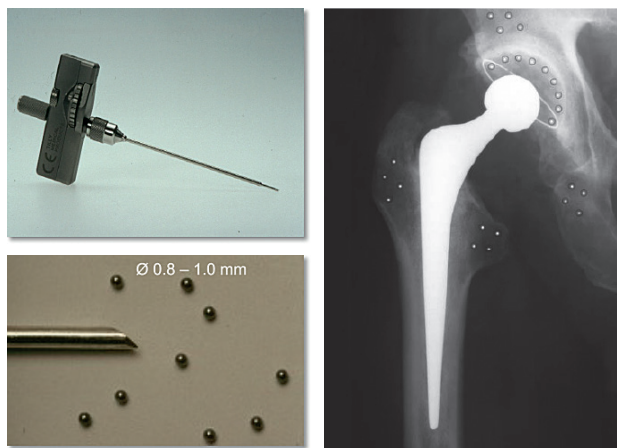
Figure 9. The highlighted tantalum markers inserted with a Tilly Medical instrument into the acetabulum, cup, and greater and lesser trochanter.
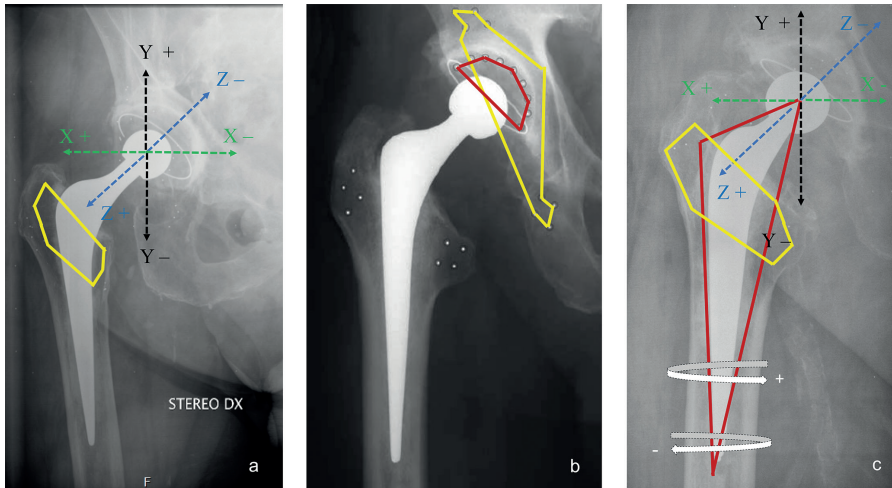
Figure 10. Radiostereometric analysis and directions of migration. The marker-based RSA method: a: point motion. b, and c: segment motion. The three cardinal axes X, Y, and Z in an orthogonal coordinate system. Migration is reported as migration along and about the three axes. The right side is considered to be standard, and for the left side the direction is changed for X-translation, and Y- and X-rotation.

The marker-based RSA method can be evaluated with either point motion or segment motion. Point motion, as used in paper I, allows calculation of only the femoral head displacement along the longitudinal, transverse, and sagittal axes, in relation to the segment of tantalum beads in the femoral bone (Figure 10a). From these three axes, a three-dimensional vector is calculated to indicate the spatial prosthetic head movement. No rotational movement can be evaluated. For the calculation of the segment motion, as used in paper IV, eight to nine tantalum beads were inserted in both the acetabulum and the polyethylene cup, thus fulfilling the requirement of at least three points in each segment (Figure 10b).

Stem displacement can also be calculated with segment motion. For this, implant manufacturers attach markers to prostheses—at the shoulder and tip of the stem. The femoral head, in combination with these markers, outlines the stem segment. The migration of the stem segment is calculated in relation to the reference femoral segment (static bone references). The segment is defined as a three-dimensional coordinate system where at least three non-linear markers are required for its definition (Figures 10b and 10c). The segment geometry allows further calculation of the prosthetic movement along the transverse, horizontal, and sagittal axes as well as calculation of any rotational movement along these axes. However, marking of the prostheses increased the cost of the implants, so a method was developed that does not require any markers on the prostheses: model-based RSA (Valstar et al. 2001,

Kaptein et al. 2003). Model-based RSA uses computer-aided design (CAD) models or models from reversed engineering instead of markers in the prosthesis. These three-dimensional surface "models" are matched on the radiographs by minimizing the difference between the virtual projection of the model with the actual projection of the prosthesis as it appears on the radiograph (Valstar et al. 2001, Kaptein et al. 2003). The model-based RSA method was not used in this thesis, so it is not discussed any further.

Furthermore, the distribution of markers within a segment is assessed using a factor called the condition number (CN), which defines the geometrical quality of each segment. A high CN indicates poor marker distribution and a low CN indicates appropriate marker distribution; a CN with an upper limit of 150 is recommended (Valstar et al. 2005). The stability of the bone markers is verified by the RSA software, which compares the inter-marker distances between consecutive radiographs. Changes in these distances are caused by measurement errors or by loosening of a marker. These changes are defined as the mean error (ME) of the rigid body, a parameter used to assess the stability of markers. The ME is the mean difference between the relative distances measured in two separate examinations. This proposal suggests that the upper limit for the ME should be 0.35 mm. Total changes in marker stability greater than 0.35 mm are considered to indicate that the marker is not stable and should therefore be excluded from the analysis. For the correct interpretation of prosthetic micromotion using RSA, the magnitude of the CN should always be related to the stability of the markers (the magnitude of the ME of the rigid body fitting) (Valstar et al. 2005).

The term "stereo" in stereophotogrammetry refers to the stereo image of the patient that is obtained, with the patient in the supine position, by two synchronized X-ray tubes at an angle to each other and in relation to the floor. By using two projections of the area of interest, it is possible to reconstruct the three-dimensional position of markers in that area. In these studies, two X-ray tubes angulated 40º to each other—and also angulated 20º to the floor—with the patient lying facilitate simultaneous imaging of the hip with the implanted tantalum markers. A calibration box placed under the patient, with similar tantalum markers positioned at known and exact positions so that they can be seen on both films, is needed to reconstruct the three-dimensional position of markers in that area (Karrholm 1989).

After the three-dimensional positions of the bone markers and the prosthesis markers have been calculated, the relative motion of the prosthesis in relation to the bone can be assessed (marker-based RSA, segment motion). The bone markers function as a reference rigid body relative to which the motion of the second rigid body, the prosthesis, is calculated. It has two fundamental modes of displacement: translation and rotation. This displacement or migration of the segment is reported as migration along and about the three orthogonal axes: the medial-lateral (X), distal-proximal (Y), and posterior-anterior (Z) directions. For the anatomical situation, the right-hand side of the body represents positive X being medial, positive Y being
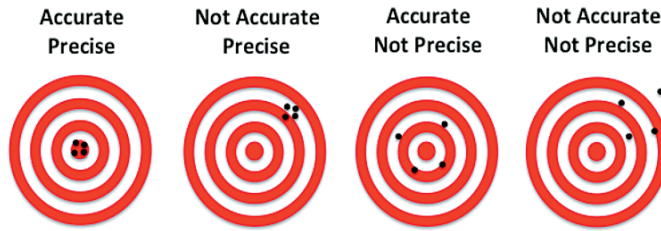
Figure 11. Schematic illustration of precision and accuracy. Accuracy is the closeness of agreement between the test result and the accepted reference (i.e. the true value). Precision is synonymous with repeatability: the closeness of agreement between independent test results obtained under stipulated conditions.

superior, and positive Z being anterior (Figure 10). Using this convention, left-hand extremities can be dealt with by reversing the X-axis for translation and the Y- and Z-axes for rotation, so that data are given in terms of anatomical directions.

The accuracy of the RSA method is used to describe the closeness of a measurement to the true value (Ranstam et al. 2000). Accuracy is determined by comparison between RSA measurements and true motion determined with a method that has no error. In reality, as no such method exists, different phantoms have been constructed to enable such determinations.

Precision is synonymous with repeatability, and is defined as the closeness of agreement between independent test results obtained under stipulated conditions. Precision is the closeness of agreement among a set of results. It should be noted that precision has nothing to do with the ability of a method to determine the true motion of an object, but rather the possibility that an exact repeat of a result can be achieved. The precision of RSA can be assessed by so-called "double examinations". Basically, double examinations are two pairs of stereo radiographs of one patient that are taken within a time interval of 10–15 min. Between the two examinations, the patient should be repositioned within limits that are expected to be encountered during a clinical follow-up study. In this short time interval, the assumption is that no real prosthetic movement has occurred; the implant should not have moved with respect to the host bone. The true relative motion between these examinations is assumed to be zero. Due to measurement errors, however, motion will be calculated, thus indicating the precision of the system (Ranstam et al. 2000). This error includes measurement inaccuracies and, if present, inducible displacement. The high accuracy and precision of the RSA method (Figure 11) are the main reasons that small-scale studies can be performed (Karrholm 1989). Because of this, RSA is commonly considered to be the gold standard technique for assessment of micromotion in joint replacement.

In both paper I and paper IV, the classic marker-based RSA method was used. During the period when patients included in paper I were operated on, the femoral implants used were not mounted with tantalum markers fixed to the shoulder and the distal tip of the stem. Nine tantalum markers, 0.8 mm in diameter, were inserted peroperatively into the greater and lesser trochanters, as scattered as possible, and the femoral head served as the stem marker. Calculation of prosthetic migration relied solely on the tantalum markers placed in the bone surrounding the implant and their relation to the midpoint of the femoral head. Thus, migration of the stem along the longitudinal axis was calculated as point motion: displacement of the center of the prosthetic head in relation to the tantalum markers in the femoral bone (Figure 10a). As no tantalum markers were present in the distal tip of the stem, rotational movement in stem migration is difficult to calculate. Also, as no tantalum markers were present in the mixture of cement and morselized bone, migration within the graft-cement composite could not be calculated separately. Migration calculated in the study corresponded to total migration along each axis.

In paper IV, 7–9 tantalum markers with a diameter of 0.8 mm were implanted in the acetabular component and another 8–9 of the same diameter were implanted into the ischial tuberosity and the acetabular roof. Once again, the marker-based RSA method was used, but the presence of tantalum markers in the acetabulum component outlined the formation of a segment. Thus, migration of the acetabular component was calculated as segment motion, even allowing the calculation along the transverse and sagittal axes as well as calculation of any rotational movement (Figure 10b). As in study I, no tantalum markers were present in the cement or morselized bone, so micromotion within the composite mixture of cement and allograft could not be calculated.

In both studies, the reference examination was performed within one week after the revision arthroplasty (paper I, range 1–5 days; paper IV, range 3–5 days), and the follow-up examinations continued for up to 9 years in paper I and for up to 2 years in paper II. Furthermore, the upper limit for exclusion of specific examinations was set at a CN of 150 and an ME of rigid body fitting of 0.3 mm.

Patient outcome and clinical assessment

The outcomes of THA can be assessed with various methods: implant survivorship, image-based assessment, clinical assessment, and patient-reported outcome measures. While the first three modalities are objective in nature, patients' reports can provide subjective measures of their perception of the success of an intervention.

Using implant revision status as a surrogate measure of functional outcome might be inappropriate, as the patient satisfaction rates following both total knee replacement (80%) and total hip replacement (90%) are both lower than their respective implant survival rates (Scott et al. 2010, Rolfson et al. 2011). Thus, omitting patient-reported outcomes precludes us from having a full understanding of the factors that contribute to pain relief, restoration of function, and patient satisfaction. For these reasons, patient-reported outcome measures are becoming increasingly important in the allocation of healthcare resources and the provision of guidelines for optimum care and management.

Today, the viewpoint of the patient is central to healthcare, and there is consensus that domains such as symptoms, function, and other considerations that are important to patients should be assessed from the patient's standpoint—and by the patient.

In Sweden, a standardized protocol including measures of health status and quality of life has gradually been introduced in both primary and revision arthroplasty. An outcome measure is used to determine the baseline function of a patient before treatment. Once treatment has commenced, the same measure can be used to evaluate progress and treatment efficacy. The outcome measure should have been shown to measure the particular aspect of health that it is purported to measure (validity) and, in the absence of any change in health, the results should be the same (or similar) regardless of who administers the test or when it is administered (reliability). Finally, measures used to evaluate outcomes should be able to detect change in status when true change has occurred (responsiveness) (Roos et al. 2011).

Patient-reported outcome measures can be divided into generic and disease-specific. In addition, patients are assessed by the orthopedic surgeon (clinician's assessment) regarding different co-morbidity burdens such as walking capacity (musculoskeletal co-morbidity), pain, and mobility (Figure 12).

Generic outcome measures include a wide range of domains, often reflecting health-related quality of life, that are relevant for a range of different diseases and populations. Specific measures involve areas of importance for a specific disease. In research, both generic and disease-specific measures are usually included, with the disease-specific measure being used as the primary outcome. The generic measure is commonly used as a secondary outcome that should support the results of the primary outcome (Table 6).
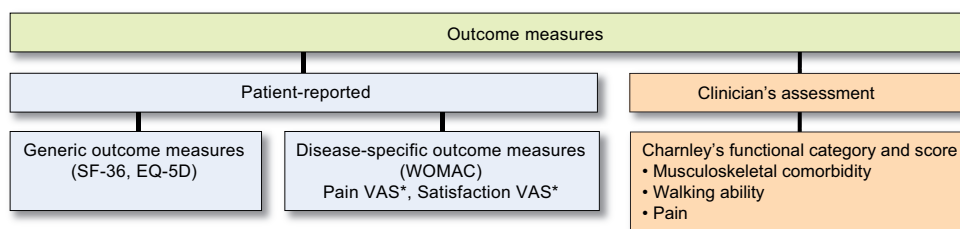
Figure 12. Outcome measure categories. *Pain VAS and satisfaction VAS, although not strictly disease specific outcome measures, as their referral question can be modified, have a referral question that is considered to be disease-specific: "rate your pain in the actual hip in the past month" and "are you satisfied with your hip prosthesis?".

Table 6. Outcome measures and their characteristics

Scale	Disease-specific	Generic outcome	Number of questions	Side-specific	Site-specific	Time frame	Score range
Womac	x		24		x	last week	0 (worst) to 100 (best)
SF-36		x	36			pain: past 4 weeks function: usual day	0 (worst) to 100 (best)
EQ-5D		x	5			today	−0.594 (worst) to 1.0 (best)
Pain (VAS)	x		1	x	x	past month	0 (worst) to 100 (best)
Satisfaction (VAS)	x		1	x	x	no time frame	0 (worst) to 100 (best)

Disease-specific outcome measures

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

WOMAC is a disease-specific measure of symptoms and activity limitations associated with hip osteoarthritis (Bellamy et al. 1991). It consists of 24 items grouped into three scales: pain (5 items), stiffness (2 items), and physical function (17 items). The WOMAC scores are standardized to range from 0 (meaning worst) to 100 (meaning best). The WOMAC is not side-specific and the time frame is "last week" for all scales.

Visual analog scale (VAS) for pain

The patients are asked to rate the severity of pain in the hip by making a mark on a 100-mm horizontal line that ranges from 0 (no pain) to 100 (worst possible pain). The exact question is "rate your pain in the actual hip in the past month". In clinical practice, the percentage of pain relief—assessed by VAS—is often considered to be a measure of the efficacy of treatment.

Visual analog scale (VAS) for satisfaction

The postoperative questionnaire includes a 100-point visual analog scale (VAS) for satisfaction. A VAS for satisfaction is a horizontal line (100-mm long) by which the patient rates his/her current health by making a vertical mark on the line. The measurement in millimeters is converted to the same number of points ranging from 0 (extreme satisfaction) to 100 (no satisfaction). Patient satisfaction has no time frame; it asks the patient to rate his or her satisfaction with the result at the time of the follow-up. The exact question is "are you satisfied with your hip prosthesis?"

Generic outcome measures

36-item Short Form Health Survey (SF-36)

The SF-36 is a generic measure of health status and quality of life. It consists of eight scales measuring physical and mental health, including a bodily pain scale (2 items) and a physical functioning scale (10 items), each of which is scored from 0 (meaning worst) to 100 (meaning best) (Ware and Sherbourne 1992). The time frame is "the past 4 weeks" for the pain scale and "a usual day" for the physical functioning scale.

EuroQol questionnaire (EQ-5D)

The EQ-5D is a generic measure of health status and quality of life. It covers five items (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), with three possible response levels (no problems, some/moderate problems, and extreme problems) (Dolan 1997). The time frame is "today". From the five items, a single weighted score is calculated, the EQ-5D index, which ranges from -0.594 (worst) to 1.0 (best). The EQ-5D also includes a 100-point visual analog vertical scale EQ-VAS, rating current health status from 0 (worst) to 100 (best).

Clinician's assessment

Charnley's functional classification

In 1972, Sir John Charnley developed a simple clinical classification system that correlated different co-morbidity burdens with walking capacity (musculoskeletal co-morbidity). For clinical assessment, the patients were classified preoperatively and postoperatively into categories A, B, and C.

Charnley category A comprises patients with unilateral hip disease, category B comprises patients with bilateral hip disease, and category C comprises those with multiple joint disease or other major medical conditions that impair walking ability. Originally, the classification was developed for use by the interviewer (Table 7).

Charnley scores

The Charnley modification of the Merle d'Aubigne and Postel score combines elements of assessment by both the surgeon and the patient. The Charnley score grades the preoperative and postoperative hip pain, mobility, and walking ability with six values ranging from 1 (meaning worst) to 6 (meaning best). Assessment of the functional component is based on the presence of a limp, the use of walking aids, and specific activities (Table 7).

Table 7. Charnley classification: category and score (The ROM value is the sum of all ranges of movements: flexion, abduction-adduction, and rotation)

Charnley classification	
Category	
A	One hip affected
B	Both hips affected
C	Both hips affected and other disorders
Score	
Pain	1 to 6 (1 = severe, 6 = no)
Walking ability	1 to 6 (1 = no, 6 = normal)
Range of motion (ROM)	1 to 6 (1 = 0°–30°, 6 > 210°)

Image-based assessment

Radiolucent lines

In clinical practice, loosening of a prostheses is assessed indirectly in successive radiographs by measuring radiolucent lines around the prosthesis and differences in position of the prosthesis relative to the bone. Radiolucent lines indicate the presence of a fibrous layer. In paper I, the presence of radiolucent lines around femoral stems was assessed in the seven zones described by Gruen (Gruen et al. 1979).

Dual-energy X-ray absorptiometry (DEXA)

DEXA scan measures bone mineral density (BMD), defined as the integral mass of bone mineral per unit of projected area. The fundamental physical principle behind DEXA is measurement of the transmission of two X-ray beams with different energy levels—one that is absorbed by the soft tissues and one that is absorbed by the bone (high- and low-photon energies)—through the body/skeleton. The amount of X-rays that pass through the bone is measured for each beam. This will vary depending on the thickness of the bone and of the soft tissues. Based on the difference between the two beams, the bone density can be measured. When soft tissue absorption is subtracted out, what remains is the patient's BMD.

The total projected area of bone is then derived by summing the pixels within the bone edges and the reported value of BMD calculated as the mean BMD over all the pixels identified as bone.

In paper IV, DEXA was performed postoperatively (range 3–5 days), at 3 months, and at 12 months. The examinations were performed in the DEXA laboratory at Lund University Hospital. Three experienced operators (who were blind regarding patients' group allocation) performed the examinations using a GE Lunar Prodigy 600 VA fan-beam densitometer (GE Medical Systems, Madison, WI, USA) (Figure 13a). Patients were scanned in supine position and the area from the lower border of the distal sacroiliac joint to an area distal to the tip of the femoral stem was included in the scan.

Bone remodeling was measured as change in BMD, from postoperatively up to 3 and 12 months. BMD was measured in four zones defined by Wilkinson et al. (Wilkinson et al. 2001) and subsequently modified by Laursen (Laursen et al. 2005), who concluded that the 4-region-of-interest (ROI) method offered higher precision (Wilkinson et al. 2001). In this model, simple rectangular regions of interest (ROIs) were created manually, as no software with predefined ROIs is available. The medial and lateral borders were created from two vertical lines; one projected along
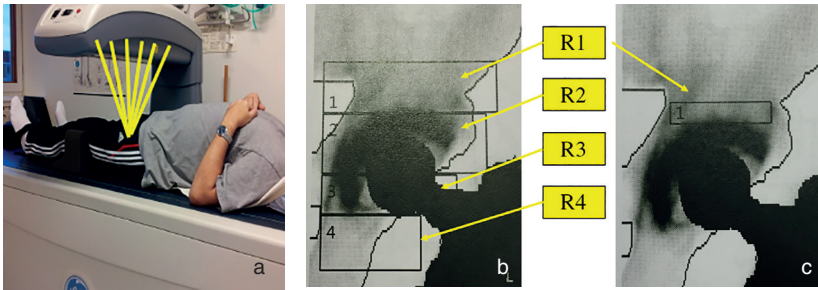
Figure 13. a. DEXA scan of a hip with a GE Lunar Prodigy 600 VA fan-beam densitometer (GE Medical Systems, Madison, WI, USA). b. 4-ROI model. c. 1-ROI model

the medial border of the obturator foramen and the other along the lateral border of the femoral prosthesis. The latter was placed as a target of the most lateral point of the ilium, to avoid femoral bone interfering with our results. The superior limit of region 1 was defined by a horizontal line 25 mm superiorly from a horizontal line touching the top border of the cup, which defined its lower limit. Region 2 extended from here to a horizontal line bisecting the center of the cup, and region 3 extended from there to the lower border of the cup. Region 4 extended from the line marking the lower border of the cup to a further line lying 25 mm below that (Figure 13b). The software paint facility was used to exclude non-bony structures. The radiopaque cement mantle was included in the analyses, since attempts to exclude it are unreliable (Wilkinson et al. 2001). No double examinations were performed during the study period.

In this study, it was assumed that high density in region 1, corresponding to the loading angle applied, is beneficial through counteracting pronounced early migration and subsequent loosening. Furthermore, the study authors considered that incorporation between host bone, allograft, and cement is less than 1 cm (10 mm); rather than the 2.5 cm (25 mm) mentioned by Wilkinson. In an effort to test the hypothesis, region 1 was re-defined and re-analyzed; the superior limit was defined as a horizontal line lying 1 cm superior to the horizontal line touching the top border of the cement and the cup, which defined its lower limit (Figure 13c).

When all ROIs had been positioned in one patient, they were copied identically and placed in the same manner in all other scans of the same individual. Two of the study authors (VZS and OB) participated in measurement of all the ROIs.

Animal study

Paper II: The effect of a biphasic injectable bone substitute on the interface strength in a rabbit knee prosthesis model.

The study was designed in order to investigate and compare prosthetic fixation and tissue integration with and without the use of injectable bone substitute in an experimental model using 16 skeletally mature rabbits. Before surgery, a protocol was made for random insertion of the prosthesis with or without bone substitute in the left or right tibia. Additionally, in a pilot study using micro-CT, we attempted to quantify the degree of bone integration and the amount of mineral around the prosthesis in four rabbits.

The tibia prosthesis

The tibia prosthesis was manufactured in one size by the Department of Medical Technology at Lund University Hospital, Lund, Sweden, and it was identical for left and right knees (Figure 14). The stem was round, straight-shaped, unpolished, 3.5 mm in diameter, and 8 mm long. A tibial plate, consisting of a titanium plate mimicking the tibial plateau shape, was mounted on the top of the stem and fixed with a screw. A rubber plug (4 mm in diameter) was placed distal to the prosthesis to prevent material leaking into the distal part of the bone marrow cavity.

Surgical technique

Both tibiae were operated on simultaneously by two surgeons (VZS and JSW), who randomly operated the left and/or the right knee with and/or without the use of Cerament fixation. A midline skin incision was made over the knee joint, which was further approached through a medial parapatellar incision. The patella was mobilized laterally, the menisci were removed, and a 1.5-mm area of the articular surface of the tibia was resected with an electric saw. The bone marrow cavity was opened with an awl and reamed with a 3.6-mm drill. Cerament bone graft substitute was used for the fixation of the tibia prosthesis on one side whereas on the contralateral control side, the prosthesis was press-fit implanted—tapped into the bone marrow using a mallet (Figure 14). After surgery, the animals were allowed to move freely in their cages and were randomly divided into two groups to be sacrificed at 6 or 12 weeks after prosthetic fixation. Four rabbits, two from each time period, were used for bone density evaluation with micro-CT.
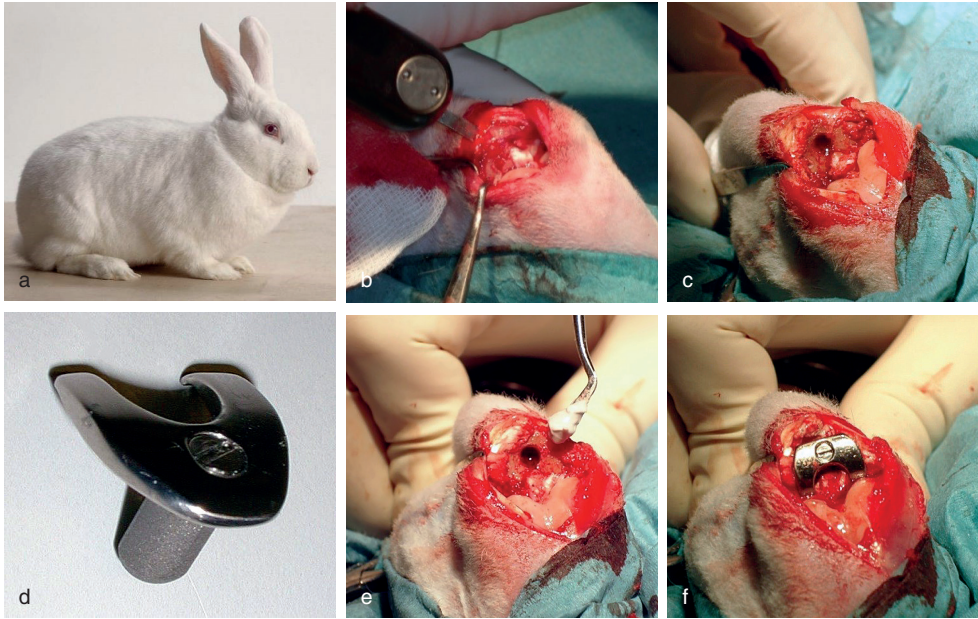
Figure 14. Surgical procedure. a. Six-month-old New Zealand White rabbit. b. A 1.5-mm area of the articular surface of the tibia was resected with an electric saw. c. The bone marrow cavity, reamed with a 3.6-mm drill; press-fit prosthesis implantation on the control side. d. The tibia prosthesis. e. Contralateral side, with use of Cerament for prosthetic fixation. f. Implanted prosthesis.

Evaluation

Pull-out test

Axial pull-out, although not a likely clinical mode of failure, is a popular experimental testing mode for evaluation of biomechanical properties of the implant-bone interface. The prosthetic tibial plate was unscrewed and replaced with a hook screwed onto the stem. The implant was first preloaded up to 1 N, and thereafter the pull-out test was performed under displacement control at 2 mm/min, with the tester being unaware of the specimen group (Figure 15). The maximum pull-out force was recorded (in N) and the data from the pull-out tests were compared for the prostheses with and without Cerament at different time points. The prosthetic failure was recorded for each specimen.
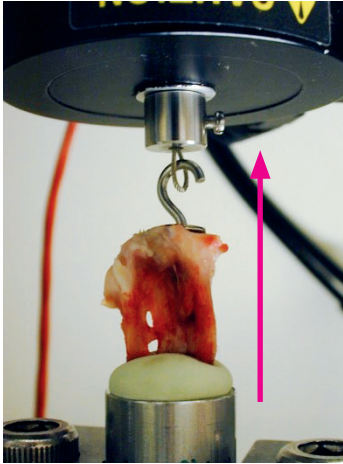
Figure 15. Pull-out test on an Instron/MTS machine. The maximum pull-out force was recorded (N) and compared for the prostheses with and without Cerament at different time points.
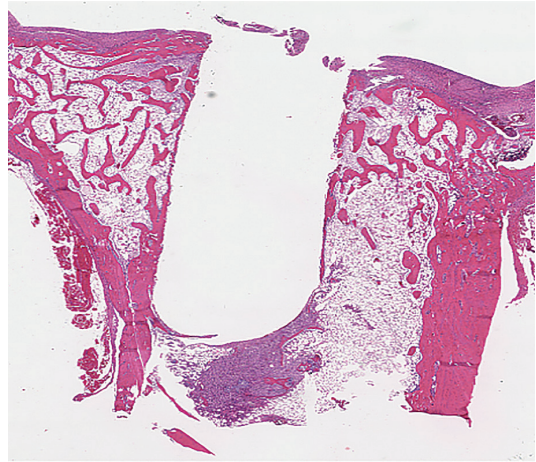
Figure 16. A section of a tibia, showing the tibial plateau, the area where the tibia prosthesis was implanted, the total bone interface length, and the detached bottom. The percentage of bone contact was calculated as the total bone contact length divided by the total prosthesis length on the sides of the implant.

Histology and histomorphometric analysis

After the pull-out test, the same specimens were prepared for histological analysis. The specimens were decalcified and embedded in paraffin. Using a diamond-edged precision saw, the specimens were cut into 5-μm longitudinal sections at 300-μm intervals. Five sections were obtained from each specimen. The microscopy sections were stained with hematoxylin and eosin. The surface area of the material remaining in the bone defect, the bone integration (measured as the percentage of the interface), and ingrowth were analyzed using light microscopy (Figure 16). All slides from one experiment were investigated in random order and in blind fashion.

The newly formed bone was marked in the histology images, and the total length of the bone interface was measured. The percentage of bone contact for each specimen in all five sections was calculated. The areas on the bottom part of the prosthesis were not included in the measuring process, since tissue had detached in some specimens during the pull-out test. The percentage of bone contact was calculated as the bone contact length divided by the total length of the prosthesis.

$$Percentage\ of\ bone\ contact = \frac{bone\ contact\ length}{total\ prosthesis\ length}$$
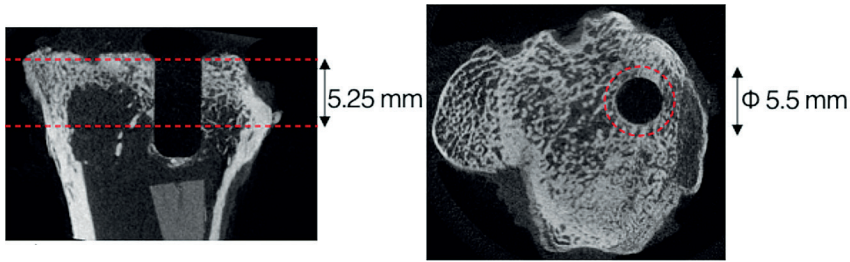
Figure 17. Micro CT images showing the region analyzed.

Micro-computed tomography (micro-CT)

Micro-computed tomography (micro-CT) is an X-ray examination used to obtain high-spatial-resolution images for three-dimensional analysis. It was introduced by Feldkamp (Feldkamp et al. 1989). The spatial resolution was about 60 μm—hence the name "micro-CT". This makes it possible to visualize individual trabeculae and to analyze the trabecular network. Further development has led to even higher resolution and the possibility of examining the connectivity and elasticity of the bone (Genant and Jiang 2006).

The micro-CT technique was used for analysis of bone density in paper III. This technique makes it possible to obtain an accurate visualization and quantification of bone microstructure. Four rabbits, two from each time period (6 and 12 weeks), were evaluated. A region 5.5 mm in diameter was analyzed, in which the 3.5 mm of the prosthesis cavity area was included. The region along the shaft of the prosthesis was analyzed for 5.25 mm (150 images) from the tibial plateau. Bone volume fraction (BV/TV) was calculated after subtracting the volume of the implant from the ROIs (Figure 17):

$$Bone\ volume\ fraction = \frac{bone\ volume\ (BV)}{total\ volume\ (TV)}$$

Statistical methods

Throughout the studies, p-values less than 0.05 were considered to be significant. The software throughout the projects was the statistical package SPSS in various versions (SPSS Inc., Chicago, IL, USA and IBM Corporation, Armonk, NY, USA). The groups in all four studies were relatively small, which is important when considering the interpretation of the clinical findings. This common limitation suggests that there would be a risk of type-2 error, i.e. failure to find a difference between groups even though a difference actually existed. Parametric tests were used when equal variances were assumed; otherwise the non-parametric equivalent was used. The small groups were also a reason for using non-parametric statistical tests, which was the case in most of the analyses.

There was also a risk of type-1 error, i.e. detection of an effect that did not exist. The risk increases with multiple comparisons. Paper II was of experimental nature and the findings were not directly applicable to clinical practice. However, the findings of papers I, III, and IV were directly applicable to clinical practice—and thus type-1 error had to be avoided. In papers I and IV, Y-migration, measured with RSA, was defined as the primary outcome variable and attempts were made to limit the number of secondary comparisons.

In paper I the mean value, the range, and the standard error of the mean (SEM) for migration along the three RSA axes were calculated. The unsigned absolute migration values used in these calculations above each cardinal axis were summed. The mean difference in migration (with 95% confidence interval (CI)) between the follow-up scores at 6 weeks, one year, five years, and nine years was calculated. For the Charnley scores, the mean and range for the preoperative and follow-up scores at five and nine years were calculated and the change in scores from preoperatively to nine years was analyzed using the Wilcoxon test. In paper II, the Wilcoxon signed-rank test was used for paired comparisons between right and left sides (at the same time point) and the Mann-Whitney U-test was used when comparing groups at 6 and 12 weeks. Results are presented as median and interquartile range (IQR).

In paper III, the analyses included calculation of the preoperative and 2-year postoperative mean scores and standard deviations (SDs) for the WOMAC and SF-36 scales, the EQ-5D index, the VAS score for health status, and the VAS score for pain. Paired t-test was used to compare the changes in scores from baseline to 2 years, and Cohen's d was used as a measure of effect size. Pearson's correlation coefficient was used to analyze the correlation between patient satisfaction score and the 2-year score, and also the change score (preoperatively to 2 years) for the other measures. The agreement between scales measuring the same type of outcome (pain or physical function) was examined using the Bland-Altman method. The internal

consistency reliability was assessed using Cronbach's alpha and the scales were examined with regard to the presence of floor and ceiling effects.

In paper IV, the primary outcome measure, cup migration, was analyzed using the Mann-Whitney U-test. In order to combine migration data from all time points throughout the 2-year follow-up period, a mixed-design analysis of variance model was also used to test for differences between groups (the clodronate and control groups). The structure of the repeated covariance matrix was defined as autoregressive (AR-1). Dependent variables were rotation and translation in each respective axis (X, Y, and Z). Main effects in the model were time and group. Interactions between the main effects were tested in separate models. The secondary outcome measure, change in proximal bone density in the ROIs, was tested using the Mann-Whitney U-test.

Limitations

Common limitations in papers I–IV

Numbers of patients

A common limitation in all the studies was the small sample size, which might restrict the extent to which the findings can be generalized. In the clinical studies (papers I, III, and IV), the aim in the study design was to have well-defined eligibility criteria, including only osteoarthritic patients with first-time revision due to aseptic loosening. This resulted in the sample size being relatively small. Although it would have been possible to use a larger sample by including all revisions performed for any reason, the findings would have been difficult to interpret.

In papers I and IV, RSA was used to detect prosthetic migration. As RSA is a highly precise method, the small number of patients studied did not jeopardize its accuracy, and therefore statistically significant findings were found.

In paper III, the sample size was adequate to show the comparative performance of the patient-reported outcome measures in that specific patient group.

Numbers of animals

The animal study (paper II) followed the rules and regulations regarding animal experiments, and used the minimum possible number of animals needed to show a statistically significant difference. The sample size of 12 rabbits was estimated to be able to reach statistical significance with similar difference and with the same power as in previous studies (Wang et al. 2000).

Common limitations in papers I and IV

RSA

A possible source of error that might be of special importance when impaction bone grafting is used is the time when the index RSA examination is performed and whether early full weight bearing is allowed.

In both paper I and paper IV, the marker-based RSA method was used. This was done despite the fact that during the period that the patients in paper I were operated on, the femoral implants used were not mounted with tantalum markers fixed to the shoulder and the distal tip of the stem. Thus, calculation of the prosthetic migration relied on the tantalum markers placed in the bone surrounding the implant and their relation to the midpoint of the femoral head. Thus, migration of the stem along the longitudinal axis was calculated as point motion. As no tantalum markers were

present in the distal tip of the stem, migration along the transverse and sagittal axes would be difficult to calculate. This was a limitation of the point motion RSA set-up used in paper I.

In contrast, in paper IV, tantalum markers were implanted not only into the ischial tuberosity and the acetabular roof but also in the acetabular component. The presence of tantalum markers in the acetabulum component outlined the formation of a segment. Thus, in paper IV, migration of the acetabular component was calculated as segment motion, allowing the calculation along the transverse and sagittal axes as well as calculation of any rotational movement.

In both paper I and paper IV, the patients had their index RSA examination within the first week after revision surgery. It would have been desirable if the index RSA examination had been performed on the first postoperative day. However, hip revision is not only associated with substantial postoperative pain—it commonly includes older patients with various associated comorbidities affecting the postoperative rehabilitation. Thus, although obtaining an RSA index examination on the first postoperative day would be desirable, it may be difficult to accomplish in such a patient cohort.

Furthermore, the postoperative mobilization regimens used in papers I and IV were not similar. During the study period when the patients included in paper I underwent revision (January 1994 to December 1995), it was unclear whether initial restriction of weight bearing was needed after hip revision with impacted morselized allograft bone. At that time, restricted weight bearing for several months after hip revision with impacted morselized allograft and cement had been the norm, in the belief that it would minimize prosthetic movements and the risk of future loosening. Thus, in paper I weight bearing was restricted for 3 months postoperatively. However, these patients also had limited activity prior to the index examination. Almost a decade later, Ornstein et al. (2003) concluded that free or restricted weight bearing after hip revision with impacted morselized allograft bone had similar effects on the stem and socket migration rates. Consequently, the patients included in paper IV were allowed weight bearing as tolerated, which also simplified the postoperative course for the patients.

Limitations in paper II

The rabbit tibia model used in paper II neither reflects a hip operation nor a revision situation; no previous prosthesis is implanted and/or extracted. Instead, it was a study of an alternative to allograft bone to be used in both hip and knee surgery. Also, neither the drilling of the tibia bone marrow in a well-controlled manner nor the lack of bone defects/loss in a primary situation accurately represents a revision situation. Furthermore, the stem of the prosthesis was unpolished. The rabbit tibia prosthesis in the group without bone substitute was inserted uncemented, creating conditions different to those addressed in the cemented human revision with allograft.
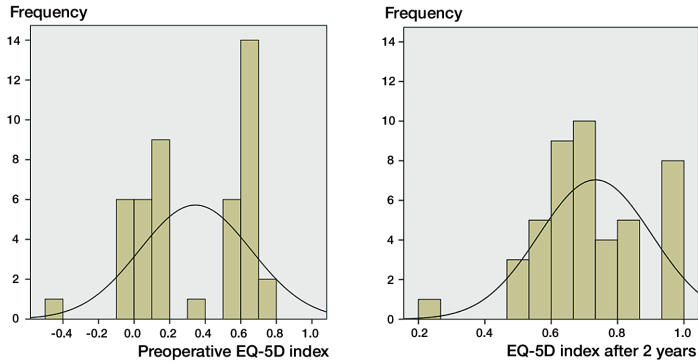
Figure 18. EQ-5D distribution at baseline and at 2 years.

Nonetheless, the use of laboratory animals in medical experiments allows the performance of surgical interventions under relatively consistent conditions. The in vivo effect can be evaluated under standardized forms—and thereafter, if significant results without any adverse effects are found, clinical applications in the form of pilot studies can be considered.

Limitations in paper III

Patient outcome

In paper III, we used the original Swedish versions of the SF-36, WOMAC, and EQ-5D, as well as the pain VAS and satisfaction VAS scales used by the Swedish Hip Arthroplasty Register—including the standard time frames for each measure. The different time frames should be taken into consideration when interpreting the differences between scale scores even when they are supposed to measure the same entity, such as pain. The same applies to whether the scale refers to the hip without side specification, to the treated hip, or to a specific location.

Moreover, the use of the EQ-5D involves some statistical issues. As each of the five domains has only three possible answers (no problem, moderate problem, and extreme problem), this results in a high probability of skewed results. The distribution of the score is known to be binominal, which makes it difficult to make meaningful comparisons between groups (Ranstam et al. 2011). In this study the distribution of the preoperative but not the postoperative EQ-5D scores appeared to be "biphasic", suggesting that the same limitation highlighted in the study by Ranstam (Ranstam et al. 2011) applies to the data, which also showed that very few patients were pain-free before revision (Figure 18).

Limitations in paper IV

Randomization

The hypothesis of the study was based upon the previous findings by Kesteris and Aspenberg (Kesteris and Aspenberg 2006). A larger study was therefore conducted in an effort to further enlighten us on the possible positive effect of bisphosphonate use in revision hip arthroplasty with morselized bone graft. The initial study enrolled patients scheduled for revision hip surgery with a cemented stem and/or cup in conjunction with impaction bone grafting. Patients were randomly divided into two groups: those in which the allograft bone was mixed with either clodronate (the treatment group) or plain saline (the control group).

When patients who met the inclusion criteria were enrolled, the initial hypothesis had further evolved, as it was considered possible that the bisphosphonate effect would differ between the femur and the acetabulum (Ullmark and Obrant 2002, van der Donk et al. 2002). Thus, the initial study population was further divided into two subgroups—those who underwent stem revision (Belfrage 2014) and those in which the socket was revised (paper IV). Thus, the randomization of the patients included in paper IV was done in a larger patient group including patients undergoing revision of both components, socket revision, or stem revision only, and not only socket revision per se.

For allocation of the participants included in both the stem study and the cup study, 36 numbered envelopes were prepared. Additionally, 36 folded papers, in two blocks of 18, with mixing instructions for bisphosphonate vial (n = 18) or buffer vial (n = 18) were prepared, placed in a box, and mixed by hand. A person from outside the study randomly selected each folded paper containing the mixing instructions, placed it randomly into one of the numbered envelopes, and sealed the envelope. These sealed, numbered envelopes containing mixing instructions were placed in a box and were chosen in numerical order during the operation by an assisting nurse. The nurse accordingly poured either clodronate or saline into a cup for later mixing with the morselized graft. The solution was prepared according to the mixing instructions in each envelope and then given to the nurse of the surgical team. This procedure meant that the assisting nurse was not blinded. This was unavoidable. However, the assisting nurse was not otherwise involved with the surgical team, and different individuals performed this task on different days. There was no way in which the surgical nurse, the surgeon, or the patient could have been informed or influenced regarding the treatment. Thus, the nurse, the patient, and the surgeon were all blinded to the randomization. In the socket study, we included 18 patients randomly divided into two groups; those in which the allograft bone was mixed with either clodronate (the treatment group, n = 9) or plain saline (the control group, n = 9). All the patients included were revised with impaction of morselized allograft bone and a cemented Exeter cup prosthesis. All RSA examinations and DEXA scans that were used in the analysis of the results were locked before the blinding was broken.

Bone mineral density (BMD)

The regions of interest (ROIs) used for the BMD analysis on the acetabulum in patients undergoing hip surgery are not standardized. No standard software is available on the market, but instead the ROIs are drawn manually around the acetabulum. Additionally, good cementing techniques in conjunction with IBG necessitate extensive penetration of cement into the interstices of the surrounding bone, thus making the line of demarcation between cement and bone indistinct. Hence, it is not simple to define each zone and this might influence the reproducibility of BMD measurements. In an attempt to minimize the error of measurement, two authors participated in the analysis of all ROIs in each patient. Another limitation was that no double DEXA examinations were performed on the study cohort; thus, the precision of the measurement analyses was not determined.

Results and conclusions

Paper I: First-time revision using impacted morselized allograft bone with a cemented Exeter stem: radiostereometric analysis of stem migration over nine years.

Study design: Prospective cohort study.

Results: All the femoral stems had migrated nine years after surgery, with migration in the distal (Y-axis) and posterior (Z-axis) directions being more pronounced than in the mediolateral direction (Figure 19). Migration of the Exeter stem in revisions with IBG occurred mainly during the first 2 years, but there was a small amount of additional subsidence up to 9 years without clinical deterioration. At the 9-year follow-up no re-revisions had been performed, no radiological loosening was seen, and the median Charnley score for pain had improved (Table 8).
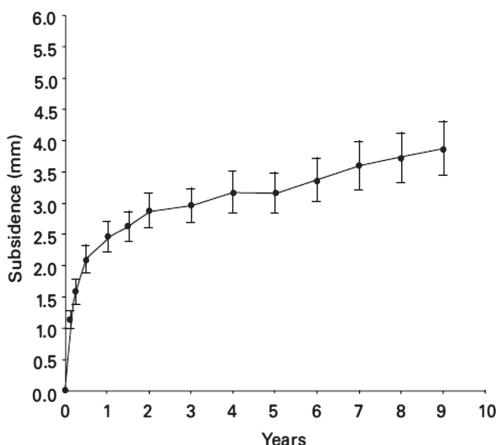
Direction	Migration (range)					Mean change (95% confidence interval) (n = 17)		
	6 wks (n = 25)	1 yr (n = 25)	5 yrs (n = 21)	9 yrs (n = 17)	6 wks to 1 yr	1 to 5 yrs	5 to 9 yrs	6 wks to 9 yrs
Distal	1.3 (0.1 to 4.8)	2.9 (0.1 to 17.9)	4.0 (0.1 to 22.8)	3.9 (0.2 to 7.8)	1.32 (0.99 to 1.66)	0.70 (0.43 to 0.97)	0.71 (0.31 to 1.11)	2.7 (2.0 to 3.5)
Mediolateral	0.5 (0.0 to 2.7)	0.7 (0.0 to 4.8)	0.9 (0.0 to 4.6)	0.7 (0.0 to 1.6)	0.15 (0.00 to 0.31)	-0.10 (-0.04 to 0.41)	-0.10 (-0.32 to 0.13)	0.2 (-0.1 to 0.6)
Posteroanterior	1.1 (0.0 to 4.7)	2.7 (0.1 to 21.0)	3.6 (0.4 to 19.6)	3.8 (0.1 to 21.7)	1.17 (0.55 to 1.78)	0.81 (0.03 to 1.59)	0.65 (-0.64 to 1.93)	2.6 (0.4 to 4.8)

Figure 19. Migration pattern of the cemented Exeter stem in conjunction with IBG. Results of radiostereometric analysis for migration of the femoral component (mean (range)).

Table 8. Clinical outcome in 17 patients followed for 9 years. Values are mean (range)

Charnley score	Preoperative (n = 17)	2 years (n = 17)	5 years (n = 17)	9 years (n = 17)	p-value Preoperatively vs 9 years
Pain	3.1 (1 to 6)	5.6 (4 to 6)	5.4 (4 to 6)	5.1 (2 to 6)	0.001
Walking ability	3.1 (1 to 5)	4.4 (2 to 6)	4.3 (1 to 6)	3.2 (1 to 6) [a]	0.9
Range of motion	4.3 (3 to 6)	4.6 (4 to 5)	4.4 (3 to 6)	4.7 (3 to 6)	0.1

[a] Charnley category (n, A: B: C) had changed from (4: 12: 1) preoperatively to (1: 8: 8) at 9 years.

Conclusions: Absolute stability is not required for good long-term outcome. Subsidence of the cemented Exeter stem after impaction bone grafting continues at a slower rate for up to nine years without clinical deterioration or radiological loosening. Continuous migration appears to be compatible with good long-term survivorship for this polished, double-tapered, collarless prosthesis design. This applies not only to revision hip arthroplasty situations but even to primary arthroplasties (Nieuwenhuijse et al. 2012a, Murray et al. 2013). However, this finding cannot be generalized to all femoral stems. Migrations should be considered in accordance with the stem design; with prostheses that are not designed to subside, continuous migration may indicate detrimental outcome (Karrholm et al. 1994).

Paper II: The effect of a biphasic injectable bone substitute on the interface strength in a rabbit knee prosthesis model.

Study design: In vivo experiment.

Results: Early prosthesis-bone interface strength (6 weeks) was not influenced by the bone substitute whereas during remodeling, the use of a bone substitute might provide improved mechanical support (Table 9, Figure 20).

Conclusions: No conclusions can be drawn regarding the use of a bone graft substitute in revision hip arthroplasty, but data regarding how it behaves in prosthetic model are presented. The results must be interpreted with caution, as the model to which the results were applied was animal-based with a well-defined bone hole—unlike the extensive bone defects present in a cemented revision surgery situation. Nevertheless, as no adverse effects (delayed wound healing, skin damage) were found with the use of bone substitute, further studies are recommended.

Table 9. Comparison of maximum pull-out force for the prostheses fixed with and without Cerament

| | Maximum pull-out force (N) | | | |
	at 6 weeks (n = 6) median (IQR)	at 12 weeks (n = 5) median (IQR)	p-value	Statistical test
Prostheses				
without Cerament	143 (78–179)	175 (115–230)	0.2	Mann-Whitney U-test
with Cerament	156 (99–210)	234 (195–243)	0.03	(between groups-time points)
p-value	0.9	0.04		
Statistical test	Wilcoxon signed rank test (between right and left side)			
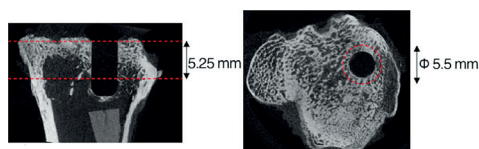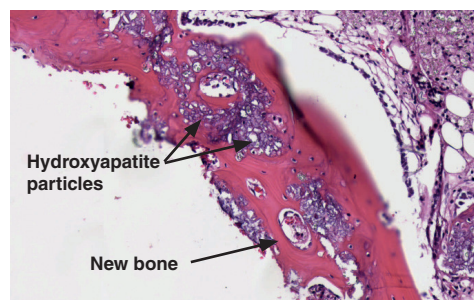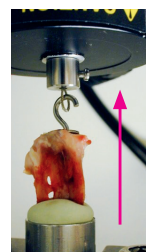
	Histology	Micro-CT
Bone contact	60–66%	
Bone fraction		35–44%

Figure 20. Histology image showing the bone interface from a prosthesis with Cerament after 12 weeks. The bone contact was between 60% and 66% at both 6 and 12 weeks, irrespective of the fixation method. The bone volume fraction (BV/TV) with micro-CT evaluation varied between 35% and 44% in the region of interest in both groups, after both 6 and 12 weeks.

Paper III: A simple visual analog scale for pain is as responsive as the WOMAC, the SF-36, and the EQ-5D in measuring outcomes of revision hip arthroplasty.

Study design: Randomized controlled study.

Results: All measures had high responsiveness (Table 10). The disease-specific WOMAC appeared to perform better than the generic SF-36 and EQ-5D in this patient group. In evaluating outcomes of revision hip arthroplasty, VAS pain is a highly responsive measure that is simple to use and it may enhance the practicality of outcome measurement.

Table 10. Scale scores before and 2 years after revision hip arthroplasty in 45 patients

Scale	Preoperatively [a]	Postoperatively [a]	Score change [a, b]	Effect size (95% CI) [c]
WOMAC				
Pain	43 (23)	81 (20)	38 (32)	1.7 (1.2–2.1)
Physical function	35 (18)	64 (22)	29 (26)	1.6 (1.1–2.1)
Stiffness	38 (21)	72 (21)	35 (34)	1.6 (1.2–2.1)
SF-36				
Bodily pain	31 (22)	61 (27)	29 (35)	1.4 (0.91–1.8)
Physical functioning	33 (22)	52 (25)	19 (29)	0.8 (0.40–1.3)
Physical role	13 (27)	38 (44)	26 (52)	0.9 (0.49–1.4)
Vitality	43 (23)	57 (26)	14 (20)	0.6 (0.62–1.1)
EQ-5D				
Index	0.35 (0.31)	0.74 (0.17)	0.38 (0.32)	1.2 (0.78–1.7)
VAS	44 (25)	73 (19)	29 (29)	1.1 (0.67–1.6)
VAS pain	63 (20)	20 (20)	–43 (26) [d]	–2.1 (–2.7 to –1.6) [d]

[a] Values are mean (SD) for preoperative and postoperative scores and score changes. Score ranges: WOMAC and SF-36 from 0 (worst) to 100 (best); EQ-5D index from –0.594 (worst) to 1.0 (best), and VAS pain from 0 (best) to 100 (worst).

[b] p < 0.001 for all comparisons, except for Physical role (p = 0.002).

[c] Effect size = mean score change divided by SD of baseline score.

[d] Negative value indicates a decrease (improvement) in VAS pain score.

Conclusions: In patients with first-time revision hip arthroplasty due to aseptic loosening, the WOMAC, SF-36, and EQ-5D showed high responsiveness in measuring patient-reported outcomes and the simple VAS for pain performed equally well. Comparison of the performance of widely used and established patient-reported outcomes in this patient category provides valuable information for researchers when they make decisions about what type of measure to select for specific uses.

Paper IV: Decreased migration with locally administered bisphosphonate in hip cup revisions using the bone impaction technique. A randomized, placebo-controlled study evaluated with radiostereometric analysis and dual-energy X-ray absorptiometry with a 2-year follow-up.

Study design: Randomized controlled study.

Results: In both groups, the magnitude of migration was small in all three directions up to two years, without any statistically significant difference between groups regarding translation along the X- and Z-axis or any rotation. There was, however, a statistically significant difference between groups regarding proximal migration (Y-axis) as shown with both Mann-Whitney U-test and mixed model analysis (Table

Table 11. Migration data at 2 years postoperatively

	Migration (mm) at 2 years clodronate (n = 9) mean (95% CI)	control (n = 9) mean (95% CI)	p-value Mann-Whitney U-test	Mixed models analysis
X-translation	0.003 (–0.09 to 0.01)	0.20 (–0.21 to 0.61)	0.3	0.6
Y-translation	0.22 (0.07 to 0.36)	0.59 (0.27 to 0.91)	0.02	0.02
Z-translation	–0.10 (–0.35 to 0.14)	–0.14 (–0.55 to 0.27)	0.9	0.9
X-rotation	0.18 (–0.11 to 0.48)	0.01 (–1.05 to 1.08)	0.4	0.4
Y-rotation	–0.06 (–0.25 to 0.11)	–0.43 (–2.12 to 1.25)	0.6	0.8
Z-rotation	–0.12 (–0.39 to 0.14)	0.32 (–0.59 to 1.23)	0.05	0.4

Proximal cup migration (y–translation)
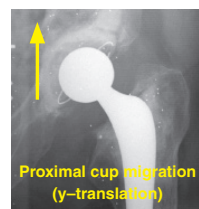
Figure 21. RSA, proximal cup migration (Y-translation). Mean values at baseline, 6 weeks, and 3, 12, and 24 months. Error bars represent the standard error of the mean (SEM).
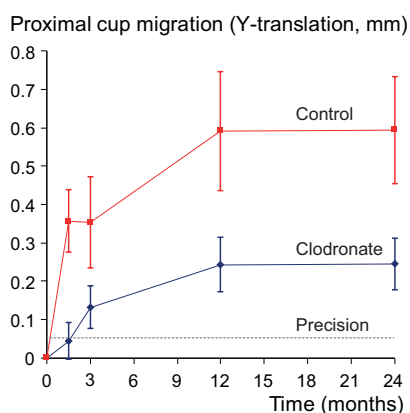
11). The efficacy of clodronate in significantly reducing cup translation compared to the controls started at 6 weeks ($p = 0.01$) and increased during the 2-year follow-up period ($p = 0.02$) (Figure 21). With mixed model analysis, the mean difference between the groups was statistically significant in the Y-translation ($p = 0.02$; 95% CI: 0.04–0.55). In the latter, there was also a significant effect of time ($p < 0.001$) (Figure 21). However, no significant differences in BMD over time between the groups could be identified.

Conclusions: Local treatment of the allograft bone with clodronate appears to result in a statistically significant reduction in proximal translation of the cup. Clodronate has an effect of delaying the initial bone graft resorption 0–6 months and allowing the graft to remodel and incorporate into the host bone, providing a more stable construct. However, this more stable construct of cement and allograft bone does not necessarily result in an increase in the BMD, as our results indicate; there were no significant differences in the BMD over time between the groups.

Discussion

Impaction grafting with allograft bone

This thesis involves two RSA studies concerning patients undergoing first-time hip revision surgery with impacted allograft bone and cement fixation. The results of these studies show that it is a well-functioning technique both with short-term follow-up (2 years) and in the long term (9 years). As shown with RSA, a gradual stabilization rather than an absolute initial fixation of the stems and/or sockets was achieved. The upper limit and time frame for acceptable migration varies depending on several factors; such as type of implant, type of fixation, and whether bone graft has been used. For some types of implants with several interfaces such as cemented stems and cups where bone graft has been used, motion may occur at the different interfaces, which makes interpretation and prediction of the migration more complicated. Nevertheless, there is no doubt that migration below the level of detection of RSA is a good prognostic sign concerning the risk of clinical loosening, even though many types of implants can tolerate higher levels of early migration.

The excellent survivorship of the Exeter femoral stem (Halliday et al. 2003, Wraighte and Howard 2008, Ornstein et al. 2009, Nieuwenhuijse et al. 2012a, Murray et al. 2013) indicates that absolute stability is not a prerequisite for good long-term outcome of implants that are designed to migrate during their lifetime. Nonetheless, if sufficient initial fixation is not obtained at the time of surgery, the implant—no matter how well it is designed—will probably fail relatively quickly. If, on the other hand, initial stable fixation is achieved but ultimately the hip prosthesis still fails, it will do this having provided the patient with a substantially improved quality of life for some time.

We believe that bone defects encountered at revision surgery should be treated biologically using a bone graft to reconstruct the skeleton. The surgically demanding operation of bone grafting is in my opinion not an objective obstacle for compromising the long-term performance of a prosthetic fixation. We accept that both acetabular and femoral implants will fail in time. If the already damaged bone bed is not reconstructed by bone graft techniques, the problems at a future revision are even worse. The survival of these cemented stems and cups after revision with this technique is very satisfying, even after a follow-up of 15—20 years (Ornstein et al. 2009, Schreurs et al. 2009, Lamberton et al. 2011, van Egmond et al. 2011, Arumugam et al. 2015).

The process of graft incorporation of impacted morselized bone grafts has been examined in biopsies and post-mortem studies of both the femur and the acetabulum (Ullmark and Obrant 2002, van der Donk et al. 2002). In general, the impacted bone graft is almost completely remodeled into new bone in the acetabulum (van der Donk et al. 2002) and to lesser extent in the femur (Ullmark and Linder 1998, Linder 2000, Ullmark and Obrant 2002). However, independently of the anatomical location in which the bone graft has been impacted, the bone graft undergoes several stages of remodeling including resorption, revascularization, new bone opposition, and finally graft incorporation.

An additional benefit of this method is that it allows the use of conventional implants, as in primary procedures—which is cost-effective.

When using the bone impaction technique with a cemented stem and cup, it is crucial not only to restore the bone stock, but also to provide a stable prosthetic construct and thus restore the mechanics of the hip. Instability of the construct can lead to premature graft resorption and subsequent implant loosening. Thus, resorption and mechanical failure are constant threats to the graft.

In order to improve and reinforce the bone graft construct and its incorporation with host bone, the use of bisphosphonates has been tried with varying results (Kesteris and Aspenberg 2006, Belfrage 2014, Saari et al. 2014). Bisphosphonates are strong anti-resorptive drugs that can improve the resistance of the allograft to mechanical load (Tagil et al. 2004). Bisphosphonates can efficiently block resorption of bone, but systemic treatment will only reach the revascularized parts of the graft. Locally administered bisphosphonates not only reduce the risk of systemic side effects, but have also been shown to remain localized and thus exert their effect where most desirable (McKenzie et al. 2011). In an animal study involving bilateral bone chambers, frozen cancellous allograft bone was implanted in 10 rats for 6 weeks. One graft in each pair had been immersed in an alendronate solution (1 mg/mL) for 10 minutes, and then rinsed in saline. Controls underwent the same treatment with saline only. The results of that study showed that at 6 weeks, the control grafts were almost entirely resorbed, but alendronate-treated grafts seemed intact (Aspenberg and Astrand 2002). Significant reduction of prosthetic migration, related to local bisphosphonate treatment, has also been shown in a 2-year follow-up RSA study of 50 patients undergoing total knee arthroplasty (Hilding and Aspenberg 2007).

In study IV, the hypothesis was that the bisphosphonate clodronate would improve the bone density in the impacted and morselized bone graft, as shown previously (Kesteris and Aspenberg 2006)—and as a consequence reduce micromotion of the implant as measured by RSA. Although anti-resorptive, bisphosphonates may paradoxically increase the amount of bone adjacent to an implant, leading to better fixation (Aspenberg 2009).

The results of the above-mentioned studies show that local application of a bisphosphonate during total joint arthroplasty surgery reduces migration. This supports the results in paper IV that early migration is dependent on osteoclast activity, and

Table 12. Implant subsidence in RSA studies of femoral revision with impaction bone grafting and a polished tapered Exeter stem. The results presented as mean values

Study	Subsidence (mm)	Follow-up (years)	Number (n)
Ornstein 2001	2.5	2	18
Nelissen 2002			
migrating group	7.5	2	18
stable group	1.2	2	18
Van Doorn 2002			
year 1	1.3	1	11
year 2	3.1	2	8
Ornstein 2004			
year 2	2.5	2	15
year 5	3.1	5	15
Zampelis 2011			
year 1	2.9	1	25
year 2	3.9	9	17
Belfrage 2014			
clodronate group	2.6	1	12
control group	2.3	1	18

that pharmacological treatment can have a measurable effect on the mechanics of total joint replacement surgery.

As shown in this thesis, the collarless, double-tapered, and polished Exeter stem used in revision with impacted morselized allograft bone and cement continues to migrate distally for up to 9 years. The most pronounced migration occurred within the first 2 years, a time period that is crucial for the remodeling stages of the bone graft (Ullmark and Obrant 2002). During the initial period when bone graft resorption and the presence of avital fibrous tissue are prominent, the lack of bone regeneration in favor of graft resorption could contribute to prosthetic migration. In this situation, a collarless femoral stem might be beneficial by gradually allowing a smooth and non-constrained positional adaptation of the stem-cement beam and might be the explanation for the initial higher distal migration. Consequently, the continuous distal migration is thought to be a sign of gradual positional adaptation of the stem-cement beam rather than being a sign of early loosening. In RSA reports on stem revision with impacted morselized allograft bone and cement, a more pronounced initial subsidence followed by migration at a low rate for at least 9 years has been observed (Ornstein et al. 2001, Nelissen et al. 2002, van Doorn et al. 2002, Ornstein et al. 2004, Zampelis et al. 2011, Belfrage 2014) (Table 12). This well-tolerated continuous migration of the Exeter stem within the cement mantle indicates that the clinical importance of early migration for the risk of later loosening differs depending on the prosthetic design, the surface finish, and the method

Table 13. Implant proximal migration in RSA studies on socket revision with impaction bone grafting and a cemented cup. The results are presented as mean values

Study	Proximal migration (mm)	Follow-up (years)	Number (n)
Franzén 1993			17
bone graft	2.7	2	7
Ornstein 1999	2.1	2	21
Ornstein 2006	2.5	5	17
Saari 2014			
risedronate group	0.3	3	15
placebo group	0.5	3	16
Mohaddes 2015			
cemented group	2.2	17	27
Zampelis 2016			
clodronate group	0.22	2	9
control group	0.59	2	9

of fixation. Thus, the presumed relationship between early migration and long-term failure caused by aseptic loosening is elusive (Karrholm et al. 2006).

There have been few publications regarding RSA-measured migration pattern of the socket in revision hip arthroplasty performed with impaction bone grafting and a cemented cup, and these have reported diverse results (Franzen et al. 1993, Ornstein et al. 1999, Ornstein et al. 2006, Saari et al. 2014, Mohaddes 2015) (Table 13). Although the impacted morselized graft with cement almost completely incorporates into new and vital bone structure in most cases (van der Donk et al. 2002), a correlation has been shown between the extent of bone defects and the rate of re-revision due to aseptic loosening (van Haaren et al. 2007). Moreover, although initial prosthetic stability is dependent on a combination of size, strength, and stiffness of the impacted chips (Bolder et al. 2003), the migration pattern of the cups is not affected by full or restricted weight bearing (Ornstein et al. 2003). However, the period of immobilization or restricted weight bearing should probably be adjusted according to the extent of the initial bone stock deficiency.

Bisphosphonates and allograft bone

Bisphosphonates may inhibit resorption of the bone next to the implant, and might also improve implant fixation when combined with allograft bone, which is in fact necrotic bone next to the prosthesis. Despite the potentially positive effect of bisphosphonates on implant fixation, there have only been a few clinical studies in this area.

The potential effect of bisphosphonates on implant fixation in humans was tested by Kesteris and Aspenberg (Kesteris and Aspenberg 2006), who combined local application of bisphosphonates with allograft bone in a 2-year follow-up study of bone density measured with DEXA. They concluded that rinsing of the morselized bone graft with bisphosphonate increased the bone density of the graft, which then remained unchanged for 2 years–and this was assumed to reduce the risk of future mechanical failure.

After that study, Belfrage (Belfrage 2014) used the same bisphosphonate (clodronate) as Kesteris and Aspenberg (Kesteris and Aspenberg 2006) as local adjunct to the bone graft in stem revisions, but he failed to show any beneficial effect. In both the Belfrage stem study (Belfrage 2014) and in paper IV, clodronate was chosen mainly because it was used successfully by Kesteris and showed a statistically significant effect on bone density, measured with DEXA (Kesteris and Aspenberg 2006). One could speculate that a stronger anti-resorptive effect might have been achieved with a modern bisphosphonate, giving a measurable increase in bone density and thus resulting in reduced prosthetic micromotion. Nevertheless, this hypothesis was not confirmed by the study by Saari et al. in which oral risedronate was used (Saari et al. 2014). On the contrary, the results from paper IV, in which local use of the less potent clodronate resulted in decreased micromotion without any significant change in the bone density, made the initial assumption doubtful.

The data from these studies do not, in our opinion, allow any general conclusions on the predictive value of the use of bisphosphonate regarding early migration and subsequent clinical failure of implants. As there are no long-term follow-up studies, the application of bisphosphonates in combination with allografts in humans should be studied in more detail. The optimal drug and the optimal concentration to be used require careful evaluation.

The use of bone substitute in revision hip arthroplasty

Cerament is an easy to use, injectable bone graft substitute that has features that are desirable in the bone remodeling process. It transforms into bone within 6–12 months (Abramo et al. 2010) and has been reported to give good clinical results related to pain reduction and bone healing (Abramo et al. 2010, Hatten and Voor 2012, Marcia et al. 2012, Nusselt et al. 2014, Kaczmarczyk et al. 2015), and also when used as a delivery vehicle for antibiotics (McNally et al. 2016). Cerament™ has a number of advantages over allograft, as it is reproducible, is easy to handle, has enhanced radio-opacity, shows rapid remodeling, and carries no intrinsic risk of infection or antigenicity. The resorption of the bone substitute must not be too rapid. A femur or acetabular component would rest upon the bone/bone substitute

construct. Since this construct is loaded during the entire remodeling phase, it is important that the transition from bone substitute into living bone takes place without an intermediary weak phase.

Two relatively recent acetabular revision studies found promising results from the use of a biphasic bone graft substitute (BoneSave, Stryker, UK)—solely, or in conjunction with impaction bone grafting (1:1 proportion) (Blom et al. 2009, Whitehouse et al. 2013). Even so, revision surgery is complex, as it includes a wide range of bone stock deficiencies, so the results of these studies must be interpreted with caution. No trials using Cerament as a bone substitute in hip revision have been published, which leaves this issue open for future exploration.

Patient outcome

There is general agreement that revision hip arthroplasty is indicated when patients seek orthopedic consultation and present with a painful hip caused by prosthetic loosening. Despite the lack of explicit criteria for hip revision, severe pain is the main indication for revision hip arthroplasty. Pain and reduced health-related quality of life are essential factors in the decision regarding surgical treatment. Thus, in the evaluation of hip replacement, pain, physical function, and quality of life should be regarded as the principal outcomes. These outcomes can be adequately assessed using patient-answered questionnaires in a more valid and reliable manner than when only outcomes recorded by the examining surgeon are available. Thus, omitting patient-reported outcomes precludes understanding of the factors that contribute to pain relief, restoration of function, and patient satisfaction.

In study III, patients undergoing hip revision surgery completed the disease-specific WOMAC and the generic SF-36 and EQ-5D questionnaires. The EQ-5D is also used by the Swedish Hip Arthroplasty Register, which later added visual analog scales for pain (VAS pain) and satisfaction (VAS satisfaction).

The results of all four questionnaires used in paper III showed substantial improvement in most health dimensions after hip revision with impacted morselized allograft bone and cement. Compared to before revision, the greatest improvements at 2 years occurred with pain, the main indication for revision surgery, physical function, and physical role.

Although it is known that disease-specific measures are more responsive than generic measures, this has not been shown in the context of revision hip arthroplasty. The measures assessed in the study are all widely used, established patient-reported outcome measures. There are many situations where it may be difficult or impractical for various reasons to use multiple patient-reported outcome measures, and researchers or clinicians may decide to choose one or more measures that serve their purpose. Furthermore, too many response categories may lead to difficulties in

choosing, whereas too few may not provide enough choice—forcing the respondent to choose an answer that is not representative of the true intent.

The VAS for hip pain and the WOMAC and SF-36 subscales for pain are different measures. In the VAS for pain used in this thesis, the patients were asked to estimate their pain without consideration of activity or rest—whereas the WOMAC and SF-36 pain subscales consist of 5 and 2 items, respectively, that relate pain to activities. Although there is some appeal in using a single score because of simplicity, reporting of outcomes in separate subscales helps in interpreting the results in clinical studies, and can assist patients in their understanding of the expected course of their recovery. However, for outcome measures with subscales, consideration of age and gender is needed for proper evaluation. An easily administered scale can be of value, especially when assessing fluctuating variables such as pain, which (preferably) should be measured repeatedly over time. Even though there is no obvious superiority of a single-scale score over an overall score from several scales, such differences are important when considering which pain measure to use and when interpreting its outcome.

We believe that showing the comparative performance of different questionnaires in this patient group provides new, valuable information for researchers when they make their decisions about what type of measure to select for a specific use.

Summary

This thesis confirms the opinion that hip revision with impacted morselized allograft bone and cement gives good patient outcomes in revision hip arthroplasty. In order to obtain these goals, stable and durable fixation of revision components must be achieved. The technique of impaction bone grafting is reliable and reproducible, with predictably favorable outcomes (Halliday et al. 2003, Schreurs et al. 2006, Ornstein et al. 2009). The original technique of impaction used the Exeter stem (Gie et al. 1993). The impacted graft is subjected to continuous loading and deformation. Thus, the use of a double-tapered polished stem appears to be a suitable option, as the stem can achieve secondary stability after subsidence. However, acetabular revision has less promising outcomes with increasing size of the acetabular defect (van Haaren et al. 2007). Unfortunately, there is no single surgical technique to solve the problem of cup fixation, as the achievement of stable initial and long-lasting fixation is challenged by the severity of different acetabular defects. Currently, the preference is biological fixation whenever possible, and alternative surgical options combined with allograft bone impaction when initial stability cannot be obtained (Rowan et al. 2016). Prerequisites for successful and durable revision include viable host bone, adequate surgical technique, and a stable and durable implant.

Since the introduction of RSA, attempts have been made to identify whether—and to what extent—early prosthetic micromotion results in later aseptic loosening (Karrholm et al. 1994). Based on the initial assumptions, stem and socket migration exceeding 1.2 mm for the stem and 1.29 mm for the socket during the first two years increases the probability of revision (Karrholm et al. 1994, Nieuwenhuijse et al. 2012b, Pijls et al. 2012). If this assumption were to be applicable irrespective of the type of implant and prosthetic fixation used, the Exeter hip prosthesis—both in primary and in revision situations—would have been withdrawn from the market, based on its RSA migration values. A one-to-one relationship between initial migration and long-term survivorship can only be assessed by long-term RSA studies, since both the initial and the long-term outcomes are known for the same patient (Nieuwenhuijse et al. 2012a). Although continuous migration of the Exeter stem appears to be compatible with long-term survivorship for this prosthesis design (Zampelis et al. 2011, Nieuwenhuijse et al. 2012a, Murray et al. 2013), this finding cannot be generalized to all femoral stems. Migration should be in accordance with the prosthetic design; for prostheses that are not designed to migrate, continuous migration may indicate detrimental outcome (Karrholm et al. 1994, Nieuwenhuijse

et al. 2012b). This necessitates the use of RSA, as a feasible tool for evaluation of existing implants and detection of inferior new implants or cements after a period of postoperative follow-up (Nelissen et al. 2011, Karrholm 2012, Nieuwenhuijse et al. 2012a, Pijls and Nelissen 2016).

Regardless of the type of implant and prosthetic fixation used, at some stage the degree of fixation, or lack of it, may cause clinical symptoms—for which the patient will seek medical consultation. At that point, for both the clinician and the patient there is (regardless of definition) a distinct difference between loose implants causing, or not causing, symptoms severe enough to warrant revision surgery. Various signs and symptoms can occur in the clinical setting of failed hip prostheses, with a painful hip being the most predominant. Groin pain therefore results in a decrease in the patient's physical function, symptoms that revision arthroplasty aims to relieve. Thus, the absolute clinical indication justifying revision hip arthroplasty is pain. However, pain as a symptom is subjective. Through physical examination and currently available evaluative tools, such as questionnaires and scales, the clinician is confronted with the task of objectifying the subjective entity of pain. For this, there is no simple solution. Considering the complexity of pain evaluation, a simple, easy to use patient-derived instrument such as pain VAS is, in my opinion, of great value—since both the initial and after-treatment scores for the same patient are known. The symptom of pain is the main determinant for a patient seeking treatment. Consequently, reducing the entity of pain determines the effect of the treatment. Other factors such as physical function, mobility, or stiffness, are related to the patient's perception of pain before and after treatment, and should therefore be considered as secondary variables when considering performing (and thereafter evaluating) a revision hip arthroplasty.

Overall, in this thesis we found that hip revisions with impacted morselized allograft bone and cement result in good clinical, radiological, and patient-assessed outcome. We found an effect of the bisphosphonate clodronate on implant micromotion, but not on bone density. Although no adverse effects were found with the use of a bone graft substitute in a rabbit knee model, carrying out further studies is to be recommended before its application in a human hip revision situation. Further research and well-designed clinical studies are needed to provide further insights regarding the optimal treatment and assessment of patients requiring revision surgery in the future.

Clinical implications

Paper I

Ongoing distal migration has generally been believed to be indicative of poor fixation, resulting in loosening. This does not appear to be the case for the Exeter stem in revision hip surgery with impaction bone grafting and cement. In fact, progressive migration is probably an important factor in the success of the Exeter prosthesis. This method can be recommended in revision hip surgery for patients with poor femoral bone stock.

Paper II

The biphasic resorption of calcium sulfate and hydroxyapatite (Cerament™) forms an osteoconductive scaffold and may lead to an early biological increase in the prosthesis-bone interface. The results indicate that this may offer an alternative treatment, which supports conducting further studies.

Paper III

In the context of revision hip arthroplasty, the simple pain VAS scale appears to be as effective as the hip-specific WOMAC outcome measure in capturing patients' main symptom: pain.

Paper IV

Local treatment of allograft bone with clodronate reduces the early proximal cup migration (RSA). This might improve cup stability, and therefore merits further study.

Summary in Swedish
Sammanfattning på svenska

För 50 år sedan började man operera utslitna höftleder och använda konstgjorda ledytor som ersättning. Antalet operationer har långsamt ökat och operationen är nu en av de vanligaste i Sverige. En ny höftled leder oftast till total smärtfrihet och ökad rörelseförmåga under lång tid men ibland kan de insatta delarna lossna. Omoperationer på grund av proteslossning ökar i antal och för närvarande utgör omoperationerna cirka 10 % av alla höftledsoperationer. Dessa är ofta betydligt mer komplicerade än förstagångsoperationer. Benbädden som protesen skulle suttit fast i skadas ofta när protesen lossnar, och detta leder i sin tur till att det är svårare att få den nya protesen att sitta fast.

En metod för att återskapa en ny benbädd är att med tät packning av malt ben återskapa benet i vilket proteskomponenterna ska fästa. Detta ben kommer från lårbenshuvuden som andra patienter donerat i samband med sina primära höftprotesoperationer. Metoden med benpackning introducerades på 1980-talet och har i många studier visat sig fungera tillfredställande under lång tid. Nytt ben återskapas och proteserna verkar ha nästan lika stora chanser att lyckas livslångt som en förstagångsoperation. Man har dock kunnat konstatera att höftproteserna efter operationen ofta sjunker ned i lårbenet, mer än vid en förstagångsoperation. Vad man inte vet är dock om proteserna därför har ökad risk för ny lossning eller överhuvudtaget kommer att ge besvär. För att ta reda på detta följde vi 17 patienter hos vilka lårbensdelen hade omopererats med benpackningstekniken. För att med stor precision och känslighet kunna följa hur väl protesen är förankrad i benet använde vi oss av en röntgenteknik (RSA), som kan registrera rörelser ned till 0,2 mm. Vi kunde då se att de fortsatte att långsamt sjunka ned i lårbenet under de 9 år som patienterna följdes men ingen patient hade sådana besvär av detta att de behövde opereras om under denna tid.

En begränsning med att använda ben från andra patienter är dels att tillgången är begränsad men också den risk för överföring av sjukdomar som finns och som kräver omfattande kontroller av det ben som skall transplanteras. Under en längre tid har man försökt att hitta konstgjorda material som kan ersätta det malda benet. Vi prövar i avhandlingen ett sådant som består av calciumsulfat och hydroxyapatit och som fått namnet "Cerament". I en försöksmodell på kanin kunde vi i studie II visa att draghållfastheten, det vill säga vidhäftningen, ökade när ett konstgjort benersättningsmaterial användes.

Man har länge diskuterat möjligheten att påverka den mekaniska stabiliteten av det ben som användes vid benpackning. Detta är särskilt viktigt när man opererar om ledskålar som lossnat från bäckenet då resultaten av dessa är något sämre än när metoden används vid omoperation av lårbensdelen. Clodronate är ett läkemedel som minskar resorption av bentransplantatet. I studie III kunde man iaktta att ledskålen rörde sig mindre efter operationen. Den ökade mekaniska stabiliteten kan leda till förbättrat långtidsresultat.

För att kunna bedöma hur patienterna upplever resultatet efter olika höftoperationer har en rad olika frågeformulär med ett antal olika frågor konstruerats. Vi evaluerade ett flertal sådana frågeformulär men ett mycket enkelt, VAS (Visual Analog Scale), visade sig lika bra som mer komplicerade formulär. Kliniskt betyder detta att det i framtida studier blir enklare att jämföra olika operationsmetoder.

Sammanfattningsvis visar avhandlingsarbetet att (i) en mindre sjunkning av proteskomponenterna i bentransplantatet inte äventyrar det goda kliniska resultatet, (ii) vidhäftningen av protes mot ben i kaninmodell kan öka med syntetiskt bensubstitut, (iii), läkemedlet clondronate blandat i transplantatet minskar sjunkningen av ledskålen in i bäckenet och (iiii) att en enkel metod, Visual Analog Scale, klarar att gradera det patientupplevda kliniska utfallet lika bra som andra mer omfattande och komplicerade frågeformulär.

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