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Periprosthetic bone and uncemented total hip arthroplasty

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Abstract

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Uncemented total hip arthroplasty (THA) has continuously increased in recent decades. Biological fixation of the implant is achieved initially by press-fit and secondary by osseointegration. However, uncemented THA is associated with loss of periprosthetic bone mineral density (pBMD), reduced mechanical strength and increased risk of periprosthetic fractures. The goals of this thesis were to study the short-term results of treatment with an antiresorptive drug for an uncemented THA (studies I and II) and the 8-year follow-up of an uncemented acetabular implant (study III). In addition, the reliability, agreement and precision for the periprosthetic standardized uptake value (pSUV) with [^{18}F] fluoride PET/CT (F-PET) were evaluated (study IV).

We conducted a randomized controlled trial (RCT) to investigate the effect of 2 subcutaneous injections of denosumab, 6 months apart postoperatively, on pBMD by dual-energy x-ray absorptiometry (DXA), pSUV by F-PET and serum markers for bone turnover for an uncemented THA with the collum femoris preserving (CFP) stem and the Continuum cup. Our results show that denosumab prevents early pBMD loss around the stem (study I) and the cup (study II), but the effect is transient upon treatment discontinuation. Additionally, denosumab reduces periprosthetic and systemic bone turnover, but the effect is unsustainable.

Study III is a prospective study to evaluate the 8-year results of the trabeculae-oriented pattern (TOP) cup in terms of implant survival, pBMD measured by DXA and clinical outcomes. We found an overall implant survival for the TOP cup of 83% and that pBMD continued to decrease in the proximal regions around the cup. The clinical outcome in patients with unrevised cups was excellent.

Study IV is a methodological study investigating F-PET's reliability, agreement and precision. 2 independent observers analyzed all F-PET scans from study II on 2 occasions, with a minimum interval of 3 weeks between each analysis. We found good reliability, high agreement and moderate precision between and within observers.

This thesis concludes that 2 doses of denosumab effectively prevent pBMD loss around the CFP stem and the Continuum cup while also reducing bone turnover. However, the effect on pBMD is not enduring, and a rebound effect on bone turnover markers appears after treatment discontinuation. Moreover, the TOP cup shows inferior 8-year survival rates compared to other uncemented implants and continuous pBMD loss proximally. Finally, the F-PET of acetabular cups can be reliably performed with strong agreement and moderate precision.

Keywords: THA, RCT, Denosumab, DXA, pBMD, F-PET

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To Melina, Philip, Sophia & Heike

List of papers

This report is based on the following papers. They are referred to in the text by their Roman numerals.

I. **Nyström A, Kiritopoulos D, Ullmark G, Sörensen J, Petrén-Mallmin M, Milbrink J, Hailer NP, Mallmin H.** Denosumab Prevents Early Periprosthetic Bone Loss After Uncemented Total Hip Arthroplasty: Results from a Randomized Placebo-Controlled Clinical Trial. *J Bone Miner Res. 2020 Feb;35(2):239-247*

II. **Kiritopoulos D, Nyström A, Ullmark G, Sörensen J, Petrén-Mallmin M, Milbrink J, Hailer NP, Mallmin H.** Denosumab prevents acetabular bone loss around an uncemented cup: analysis of secondary outcomes in a randomized controlled trial. *Acta Orthop. 2022 Sep 7;93:709-720*

III. **Kiritopoulos D, Nyström A, Hailer NP, Mallmin H, Lazarinis S.** Continuous periprosthetic bone loss around the TOP® cup and inferior survival rate at an 8-year follow-up: A prospective cohort study. *BMC Musculoskelet Disord. 2024 Sep 16;25(1):741*

IV. **Kiritopoulos D, Nyström A, Mallmin H, Hailer NP, Ullmark G.** Assessment of Bone Metabolism Around Uncemented Acetabular Hip Implants: Good Inter- and Intraobserver Reliability and High Agreement of Periprosthetic F-PET. *Submitted*

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Contents

Abbreviations

AE	Adverse event
AFF	Atypical femoral fracture
ANCOVA	Analysis of covariance
BMD	Bone mineral density
BP	Bisphosphonate
BTMs	Bone turnover markers
CFP	Collum femoris preserving
CT	Computed tomography
DXA	Dual energy x-ray absorptiometry
EBM	Evidence-based medicine
EQ-VAS	EuroQol visual analogic scale
F-PET	[^{18}F] sodium fluoride positron emission tomography/CT
GCP	Good clinical practice
HHS	Harris hip score
ICC	Intraclass correlation coefficient
KM	Kaplan-Meier
mSv	milliSievert
OA	Osteoarthritis
OAH	Osteoarthritis of the hip
OPG	Osteoprotegerin
PE	Polyethylene
P1NP	Procollagen type 1 N-terminal propeptide
pBMD	Periprosthetic bone mineral density
PROMs	Patient-reported outcome measures
pSUV	Periprosthetic standardized uptake value
PTH	Parathyroid hormone
QoL	Quality of life
RANK	Receptor activator of nuclear factor-Kappa-B
RANKL	Receptor activator of nuclear factor-Kappa-B ligand
RCT	Randomized controlled trial
RSA	Radiostereometric analysis

SAE	Serious adverse event
SUV	Standardized uptake value
THA	Total hip arthroplasty
TOP	Trabeculae-oriented pattern
UHMWPE	Ultra-high molecular weight polyethylene
VOIs	Volumes of interest

Introduction

Osteoarthritis

Osteoarthritis (OA) of the hip (OAH) is a widespread, degenerative disease accompanied by stiffness, restricted range of motion, hip pain and reduced quality of life (QoL). OA is characterized by loss of cartilage, subchondral bone remodeling, joint space narrowing, development of osteophytes and synovial inflammation. Increasing age is the main risk factor for developing OA, but genetic factors, obesity and high levels of joint loading contribute as well [67].

The initial treatment of OA includes lifestyle modifications, such as weight loss, exercise, patient education, physiotherapy and pharmaceutical treatment with analgesic and anti-inflammatory drugs [102]. In most patients, clinically significant OA of the hip that does not respond to conservative treatment is treated with a total hip arthroplasty (THA).

Bone biology

Bone is a dynamic tissue normally renewed through balanced bone formation and resorption processes. The ability of bone to remodel is important to the structural and metabolic properties of the skeleton. It consists of cells (about 2% of bone tissue) and extracellular matrix (about 98% of bone tissue) [139]. 3 cell types can be found in bone: the bone formation osteoblasts, the tissue resorption osteoclasts and the osteocytes. The osteocytes derive from osteoblasts, accounting for 90% of the adult skeleton [139]. The main function of the osteocytes is to orchestrate the spatial and temporal recruitment of the cells that form and resorb bone. Frost et al. introduced the term mechanostat, a regulatory mechanism by which bone tissue adapts to mechanical loading [45]. According to that theory, osteocytes act like sensors that detect the mechanical loading on bone. Bone with overload, such as exercise and weight-bearing activities, stimulates bone formation and strength, while bone not being used decreases bone mass and strength [7, 66]. The extracellular matrix is composed of 30% organic substance (mainly collagen type I) and almost 70% mineral (hydroxyapatite) [113].

Bone is constantly being remodeled throughout adult life and in the growing skeleton, and there is a coupling between osteoblasts responsible for building new bone and the osteoclasts responsible for the removal of fully mineralized bone. An imbalance in this procedure, with an increase in the action of the osteoclasts compared to that of the osteoblasts, leads to a net decrease in bone mass, a common phenomenon in postmenopausal women and older men. Advanced age poses a risk for the development of osteopenia, indicated by a decrease of 1 SD to -2.5 SD, as well as osteoporosis, characterized by a decline of -2.5 SD or more below the reference value of bone mineral density (BMD) in young adults [165]. Furthermore, it is also associated with frailty, a clinical state characterized by diminished health and functionality among older individuals [35]. Low BMD and frailty affect bone strength and increase fracture risk [28, 126]. Bone remodeling occurs in specific remodeling sites called bone multicellular units (BMUs). Remodeling is higher in the trabecular bone than the cortical bone. Bone remodeling is initiated at the BMUs by the osteoblasts, which activate osteoclasts to start bone resorption. When the osteoclasts have resorbed bone and built up a gap under the resorption phase, they disappear and "cleaning cells" (mononuclear macrophage lineage cells) arrive to destroy the rest of the bone matrix and prepare the surface for bone formation. During the resorption phase, coupling factors are secreted, stimulating and recruiting osteoblasts to fill the gap and start bone formation. Under physiological conditions, osteoblasts build the same amount of absorbed bone. The remodeling process ends with the mineralization of the surface [19].

Besides the osteoblasts, osteoclasts and osteocytes, other mediators of bone metabolism exist to maintain bone homeostasis, such as hormones, cytokines and various cells regulating bone formation and resorption. Osteoprotegerin (OPG) acts as a regulator of bone remodeling by inhibition of the receptor activator of nuclear factor – Kappa (RANK) through the RANK-ligand (RANK-L) mechanism, thus affecting the maintenance of the correct balance between bone resorption and formation (figure 1) [34]. Wnt proteins that act through the Wnt pathway are crucial in activating osteoblasts, leading to increased bone formation [73]. Inhibitors of the Wnt pathway, such as sclerostin, reduce bone formation. Parathyroid hormone (PTH) stimulates osteoclast-mediated bone resorption, whereas estrogens inhibit osteoclast and promote osteoblast survival [131].

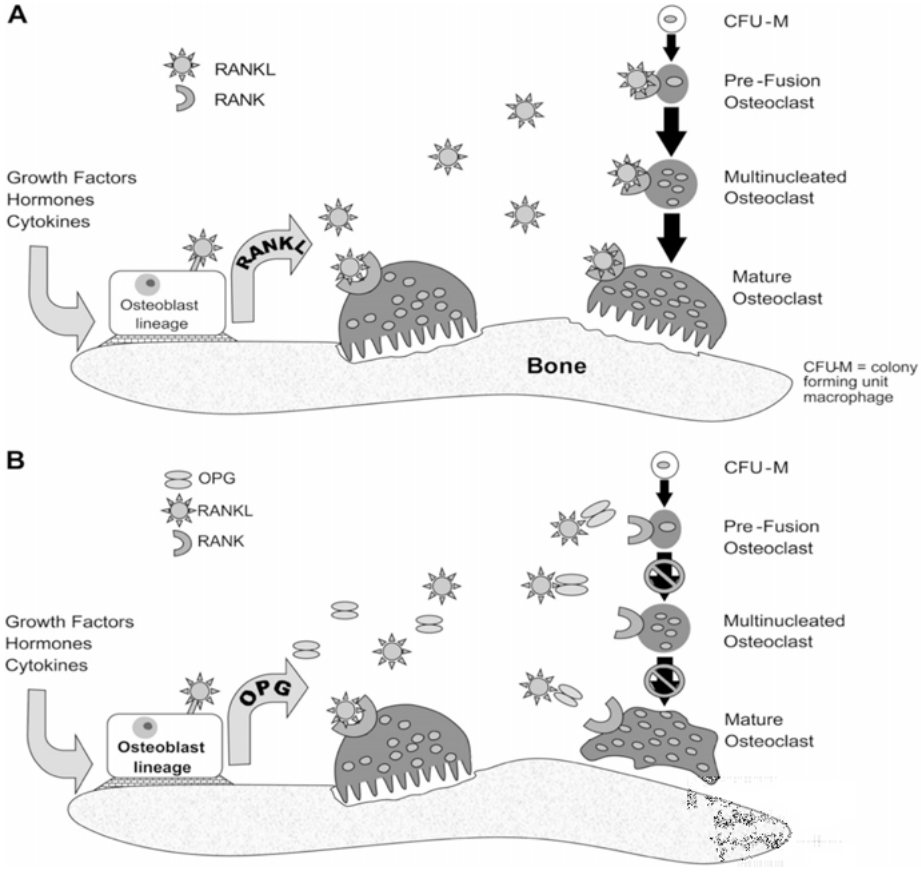

Figure 1. (A) Role of RANK and RANKL in bone remodeling. (B) Regulation of RANK/RANKL binding by OPG.

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The fundamentals of bone remodeling are referred to as Wolff's law, which states that mechanical forces are among the most potent factors influencing bone resorption and formation. As a consequence, BMD in a bone that is not loaded will diminish and BMD in bone that is loaded will increase [22, 46].

Periprosthetic bone mineral density (pBMD) loss around the acetabular cup and the femoral stem has been reported after uncemented THA [36, 82, 84, 108]. This pBMD loss is mediated initially by postoperative trauma-induced inflammation and later by osteoclast activation and mechanisms such as stress shielding, polyethylene (PE) liner wear, implant material and stiffness. The type of fixation (cemented or uncemented) affects this phenomenon [142].

The dynamics of acetabular pBMD around trabecular acetabular implants are still controversial, but studies on cemented and uncemented cups indicate a reduction of pBMD [36, 85]. An association has been observed between

periprosthetic osteolysis in uncemented THA and implant failure on the acetabular side [57, 143]. In osteolysis, the dominant mechanism for bone degradation is the inflammatory response to wear debris, mainly from PE liner [60]. This debris is phagocytosed, activating the macrophages and osteoclasts, resulting in bone resorption [112]. However, the clinical importance of proximal pBMD loss and osteolysis around the uncemented cups remains unclear.

An alternative explanation for aseptic cup loosening is the theory of early implant loosening [96]. According to this theory, implant loosening has already been initiated during or shortly after surgery due to poor interlock between the bone and the implant or poor bone quality. Micromovements of the implant cause high fluid pressure between the bone and the implant, inducing periprosthetic osteolysis by a series of inflammatory responses.

At the femur, pBMD loss is observed mainly in the proximal regions due to stress shielding, i.e., the mechanical load is transferred distally through the implant, unloading the proximal regions. Loss of pBMD is a surrogate variable for possible implant loosening, but the clinical importance is still uncertain [13, 106, 136, 161]. Aseptic implant loosening is accompanied by loss of pBMD, often diagnosed through conventional X-ray imaging.

Total hip arthroplasty and uncemented hip implants

With 10-year implant survival rates above 95% and enhanced QoL, THA is an exceptionally successful intervention [63]. The incidence of hip replacement has increased continuously over the past decades worldwide. In Sweden, more than 20,000 THAs were performed in 2022, of which 89% were due to primary OA [166]. The results are excellent, with almost 95% of the implants still in place after 10 years and nearly 80% after 20 years [166].

Most patients operated on with a THA are older adults. In Sweden, implants are preferably fixed to the bone with cement for this category of patients. The fixation of the prosthesis to the bone relies on cement intrusion into the porosity of cancellous, trabecular bone [166].

The implant is often fixed directly to the bone without cement in younger patients with good bone stock. The use of uncemented fixation in hip implants has continuously increased in Sweden during the past decades [166]. Biological fixation is achieved by initial press fit, which secures the primary stability of the implant. Secondary fixation is achieved by osseointegration, where a bond between the bone and implant occurs. Younger patients have a longer life expectancy and higher activity demands, leading to increased loads per time unit for implants and fixation. Although improving, the 10-year survival rates for uncemented THA, often preferred for younger and middle-aged patients, are less favorable than cemented THA in older people [54, 166]. The trend in THA is operating younger patients, which leads to an increase in the

use of uncemented implants. Consequently, an increasing number of patients could be expected to need revision surgery in the future [166].

The most common failure mechanisms leading to revision are aseptic loosening of the implant, infection, periprosthetic fractures, liner wear and dislocation [41, 70, 166]. Aseptic loosening of the implant, being the most frequent cause of failure after THA, often occurs many years after the index surgery. Revision surgery due to dislocation and infection, the second and third most frequent causes of failure, is usually performed early after index surgery (within 5 years) [31, 155].

Mineralized bone loss occurs in specific zones around the implant. This can be visible on plain X-ray images and quantified as pBMD, measured by dual-energy X-ray absorptiometry (DXA).

Acetabular implants

The 2 most common types of uncemented cups are mechanically fixed by press-fit or threads, although the latter is not used as often. Primary stability is attained in both types through form-fitting geometry and frictional engagement. In modern uncemented THA, the form of the cups is usually hemispherical, preserving the subchondral bone and leading to excellent adaptation [120]. The shell of the cups is composed of different metals or alloys, often from titanium. For some, the outer surface is slightly rough to improve fixation ingrowth of bone. Others have coated the outer surface with low-calcium hydroxyapatite (HA) precursor brushite, believed to enhance bone ingrowth, stimulate bony gap closure and achieve improved secondary stability. Both brushite and HA are calcium phosphate compounds but differ in chemical composition and biological properties. Brushite is a hydrated form of calcium phosphate, less stable and more soluble than HA, quickly solvable when implanted in the body. On the other hand, HA is a stable crystalline form of calcium phosphate, much less solvable. Many cups are also provided with holes to enable the use of screws for additional stability. Nevertheless, the use of holes without screws has raised controversy due to a potential "pump mechanism" that may heighten the risk of osteolysis [16]. The cups are commonly modular with the option of liner exchange. There are many different liners, with PE being the most widely used. The initial ultra-high molecular weight polyethylene (UHMWPE) has evolved to the more resistant to wear debris highly cross-linked PE with enhanced mechanical properties [18, 104]. To reduce oxidation, the development of highly cross-linked PE stabilized with vitamin E emerged [114]. Other types of liners include ceramic and metal. Ceramic liners are believed to reduce wear debris better than PE liners, but scratching and fractures on the liner can occur. Moreover, they are more expensive, and in a multicenter, randomized, prospective study, ceramic-on-ceramic articulation showed no significant clinical difference from metal-on-PE

bearing [21]. Metal liners have been used frequently in the past. Metal-on-metal articulation demonstrates lower numbers of wear debris than metal on PE bearing, but aseptic lymphocyte-dominated vasculitis-associated lesions (ALVALs) [27, 32] and sometimes carcinogenesis is observed [129, 132]. Because of that, metal-on-metal articulation is restricted in many countries nowadays, as seen in registries [166]. However, extensive epidemiological studies have not demonstrated a correlation between THA and cancer development [55, 56].

Cup failure has also been observed due to the poor locking mechanism of the liner, leading to PE wear and, thus, extensive osteolysis [57, 81, 143].

Stems

In uncemented THA, the mechanical properties of the stem, which are provided by its shape, are crucial for stem stability. There are three broad categories of stems: cylindrical, anatomical and tapered. Cylindrical stems are canal-filling and need increased size to achieve distal cortical support and gain stability. Increased stem diameter increases stem stiffness, which could lead to cortical atrophy, proximal stress shielding, thigh pain, and, consequently, periprosthetic fractures [69]. Anatomical stems are developed with an anteroposterior curvature to imitate the femur's natural anatomy and physiological loading, thus reducing stress shielding [52]. Tapered stems use a 3-point fixation to obtain immediate stability [116]. A recent classification by Kheir et al. categorized the uncemented stems into types based on design and morphology: short stems, conventional straight stems by increasing fixation (single-wedge, double-wedge, tapered, cylindrical), modular and anatomical [72].

The extent and distribution of pBMD changes in uncemented THA differ between different stem types [13, 136]. Stem fixation with close cortical contact in the diaphysis is associated with distal loading, stress shielding and proximal bone loss. Moreover, the preservation of proximal bone stock is important for revision surgery. These factors have led to the necessity of developing short stems that preserve the proximal bone. Besides preserving bone integrity, short stems theoretically include benefits such as reduced incidence of thigh pain due to minimized diaphyseal engagement and fixation within the metaphyseal bone, mitigating stress-shielding effects.

Hip resurfacing was introduced as an alternative to preserve mostly proximal bone. Hip resurfacing is a metal-on-metal articulation with a large caput, leading to significant friction and is associated with complications such as femoral neck fracture, early loosening and ALVALs [27, 32]. Short femoral stems were introduced to preserve bone in the proximal part of the femur without complications related to hip resurfacing.

Besides the shape, uncemented stems can have different surfaces. Many porous-coated stems are made of cobalt chromium (CoCr). However, this alloy is stiffer than bone and may induce bone remodeling of the periprosthetic bone. Titanium, known for its high biocompatibility, is commonly used in the construction of most stems. However, the alloy of these stems could be from titanium, aluminum and vanadium. Titanium has a higher elasticity than CoCr, which could lead to a reduction in stress shielding. Examples of stems composed of titanium include the CFP, Corail and Bimetric stem. The surface of the titanium is always treated with "grit blasting," a process used to clean, prepare and modify the surface of implants. The roughened surface of the implant created by grit blasting improves its osseointegration. The use of HA surface has also been proposed to enhance bone ingrowth and result in better fixation and improved long-term results [48, 123]. However, register studies do not support this proposal [82, 83].

Clinical trials

Clinical trials encompass research that studies new drugs, tests and treatments and evaluates their effect on humans [127]. They are the gold standard for testing medical interventions, including medications, biological products, surgical and radiological procedures, behavioral treatment and preventive care. Clinical trials are carefully designed, monitored and completed and need approval from national competent authorities and ethics committees before they start.

There are four phases of clinical trials [156]:

- Phase I studies are usually small studies that recruit a few people and test a new drug for the first time in humans. The main concerns of Phase I studies are establishing a new drug's safety and dosage range and identifying potential side effects. They often use dose escalation studies to determine the most effective dose without producing unacceptable side effects.
- Phase II studies test treatments that are safe in Phase I but now need a larger group of human participants to monitor for any adverse effects. They aim to determine the effectiveness of an experimental drug on a particular disease or condition in approximately 25-100 volunteers. Most Phase II studies are randomized and often double-blind, preventing any unscientific influence on the study results that can be caused by knowledge of the treatment. The duration of these studies is from some months up to 2 years.

- Phase III studies compare the safety and effectiveness of the new treatment against the current standard treatment. They are conducted on larger populations (several hundred to several thousand patients) in different regions and countries.
- Phase IV studies take place after the approval of the drug, further evaluating the drug's effect, benefits and side effects.

Evidence-based medicine

Physicians invariably seek to base their decisions on the best available evidence. Evidence-based medicine (EBM) entails applying the best available research to clinical care, which requires integrating evidence with clinical expertise and patient values [25]. Scientific evidence includes study outcomes and opinions, but not all data have the same strength. The level of evidence or data should be graded according to their relative strength. Stronger evidence should be given more weight when making clinical decisions.

The evidence is usually stratified into six levels [20] (figure 2).

- Level IA evidence is obtained from a meta-analysis of multiple well-conducted and well-designed randomized trials. Randomized trials provide some of the strongest clinical evidence. If these are repeated and the results are combined in a meta-analysis, the overall results are assumed to be even stronger.
- Level IB evidence is obtained from a single well-conducted and well-designed randomized controlled trial (RCT). When well-designed and well-conducted, the randomized controlled study is a gold standard for clinical medicine.
- Level IIA evidence is from at least one well-designed, executed, non-randomized controlled study. When randomization does not occur, more bias may be introduced into the study.
- Level IIB evidence is from at least one well-designed case-control or cohort study.
- Level III evidence is from at least one non-experimental study. Typically, it would include case series, not well-designed case-control or cohort studies.
- Level IV includes expert opinions from respected authorities based on their clinical experience.

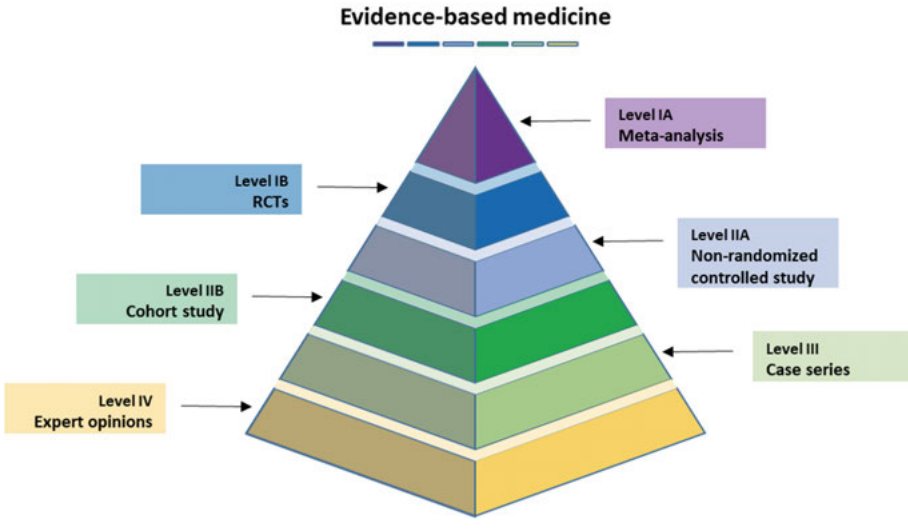


Figure 2. The levels of evidence-based medicine.

Pharmacological interventions

pBMD loss is a potential risk factor that could influence implant stability and increase the risk of revision surgery in uncemented THA [13, 106, 136, 161]. Regimes to overcome pBMD loss have been proposed, including treatment with antiresorptive drugs, (e.g. bisphosphonates), but these have only provided a transient positive effect on pBMD [44, 101, 137].

Several drugs have shown effects on bone turnover, seeking to increase BMD and reduce the risk of fractures. Several such drugs are approved and widely prescribed for osteoporosis and metabolic bone disease [12, 30]. 2 mechanisms are available to achieve increased BMD: inhibition of bone resorption or stimulation of bone formation.

The most widely used drugs are bisphosphonates (BPs), which have a strong antiresorptive effect on bone tissue. They have a high affinity to bind to bone minerals and osteoclasts. BPs reduce bone resorption by inhibiting osteoclastic activity and shorten their life span by increased apoptosis [43]. Nitrogen-containing BPs (such as alendronate, zoledronate and risedronate) inhibit the mevalonate pathway by preventing protein prenylation, essential for osteoclast function and survival. This inhibition leads to osteoclast apoptosis [89]. Non-nitrogen-containing BPs (such as etidronate and clodronate) are metabolized within osteoclasts, replacing molecules producing malfunctioning ATP analogs. These analogs are believed to be cytotoxic for osteoclasts, leading to osteoclast apoptosis. Non-nitrogenic BPs are less potent than nitrogen-containing BPs and have fallen out of widespread use [39]. BPs are

used clinically to treat osteoporosis by increasing BMD, suppressing or reducing markers for bone turnover and ultimately preventing fractures [12, 58, 88, 90]. Several studies have reported the effect of BPs on bone remodeling adjacent to orthopedic implants and have found a positive but, unfortunately, only a temporary bone-sparing effect [137, 158, 164]. After cessation of the drug, BMD tends to decrease.

Another pathway to inhibit bone resorption involves using a human monoclonal antibody, denosumab, with osteoprotegerin-like action (figure 1). It was introduced to the market in 2010 and is administered as a subcutaneous injection every 6 months. This makes compliance less of a problem compared to oral BPs, which often have compliance of less than 50% after 1 year of treatment due to difficulties following the specific 1-2 hours of fasting restriction after oral intake of the drugs and gastrointestinal side effects [87]. Denosumab mimics the effect of OPG on RANK-L by blocking the RANKL-ligand complex, rendering fewer osteoclasts, malfunctioning them and leading them to apoptosis [15] (figure 1). A 60 mg denosumab injection every 6 months increases BMD and reduces bone turnover and fracture risk [30]. At the time of initiation of our study, there were no reports on the effects of denosumab on pBMD. Before our study, reports indicated a loss of gained BMD and a rebound effect on biochemical markers of bone metabolism in postmenopausal women with osteopenia or osteoporosis 12 months after discontinuation of 24-month treatment with denosumab [14, 95]. After the start of our study, several case reports and post hoc analyses on the extension of the randomized controlled Freedom study reported increased incidences of vertebral fractures after discontinuation following several years of treatment with denosumab. [2, 6, 29]. The effect of withdrawal after only 2 doses of denosumab on pBMD is still unknown, and no increased fracture incidence has been reported.

In the past few years, a new human monoclonal antibody, romosozumab, was introduced to the market for treating osteoporosis. Romosozumab binds and inhibits sclerostin, an inhibitor of bone formation secreted by osteocytes and permits signaling along the Wnt pathway, with a dual effect of increasing bone formation and decreasing bone resorption. Systematic reviews show that romosozumab increased BMD at the lumbar spine, total hip and femoral neck, significantly reducing the incidence of vertebral, nonvertebral and clinical fractures in postmenopausal patients with osteoporosis [26, 134]. No reports have been published for controlled trials with romosozumab on pBMD.

BMD can also be increased by enhancing bone formation with PTH. Teriparatide is a PTH analog used in the treatment of osteoporosis. Daily subcutaneous injections with teriparatide stimulate osteoblasts, causing an increase in BMD and reduced risk for vertebral fractures [105]. In one RCT, daily subcutaneous injections of teriparatide for 48 weeks resulted in an equally positive effect of femoral pBMD as alendronate [77].

Radiographic outcome measures

Radiography

Preoperatively, anteroposterior (AP) and lateral radiographs of the hip and AP of the pelvis are obtained for the degree classification of OAH and operation planning [68]. Postoperatively, similar radiographs are obtained to evaluate implant positioning and, in the long-term, to determine signs of implant migration, periprosthetic radiolucent zones, osteolysis, signs of PE wear and periarticular heterotopic ossification [117].

Computed tomography (CT)

CT is an alternative to X-ray imaging diagnostics. It allows for the creation of detailed 3-D images with good resolution. In the past years, combining 2 or more CT images has been used to calculate the difference in relative position between the pelvis and implant, allowing for the detection of implant micromotion [110].

Dual-energy X-ray absorptiometry (DXA)

Antero/posterior DXA is the gold standard method for quantifying and measuring the areal BMD quickly and precisely. This method has been used to measure BMD in the lumbar spine and proximal femur for more than 30 years to diagnose osteoporosis and predict fracture risk [65, 92]. DXA has been used in the orthopedic field to measure BMD around implants. Around the acetabulum, the three DeLee and Charnley zones have frequently been used to measure BMD [33] and around the stem, the seven Gruen zones [53]. The acetabular zones described by DeLee and Charnley and the femoral zones described by Gruen were originally developed to classify the radiolucent lines between the implant and bone after THA. Another classification to measure BMD around the acetabulum involves the use of the five Digas zones [36] (figures 3 and 4).

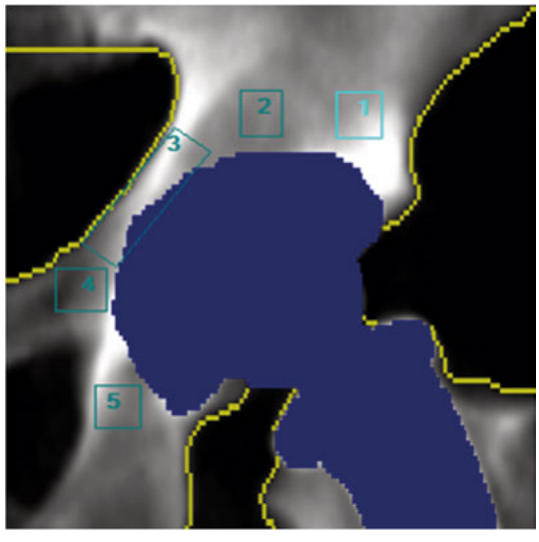


Figure 3. According to Digas, the DXA scan shows the 5 zones around the Continuum cup.

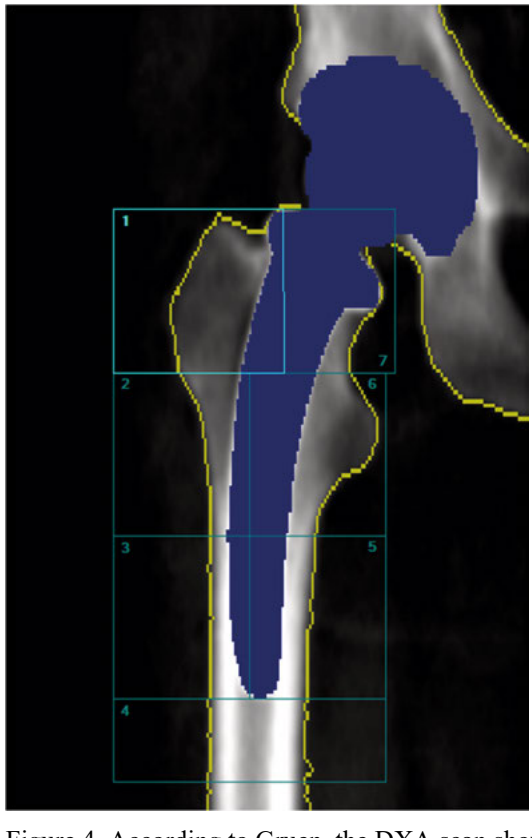
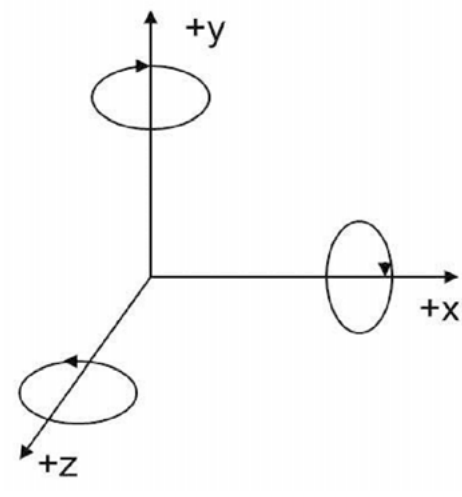


Figure 4. According to Gruen, the DXA scan shows the 7 zones around the CFP stem.

Radiostereometric analysis (RSA)

Radiostereometric analysis (RSA, also known as radiostereometry and roentgen stereophotogrammetric analysis) was initially developed for orthopedic research by Selvik [128]. During the 1980s and 1990s, RSA became the golden standard for implant research and THA evaluation [91]. RSA is a highly precise imaging technique used to measure the micromovements of implants and evaluate their stability. Tantalum markers are inserted into the bone and in the acetabular implants during surgery. The stem is provided with tantalum markers inserted by the manufacturer. These markers in the bone and the implants form rigid bodies. 2 X-ray tubes are used simultaneously with an angle of 40° to take the RSA radiographs. These images capture the position of the rigid bodies. With the use of software, the movement of the implant relative to the bone can be calculated in three axes with exceptional precision [157] (figures 5 and 6).



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

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

Figure 5. Rotation around and translation along three axes in radiostereometric analysis. Courtesy of Stergios Lazarinis.

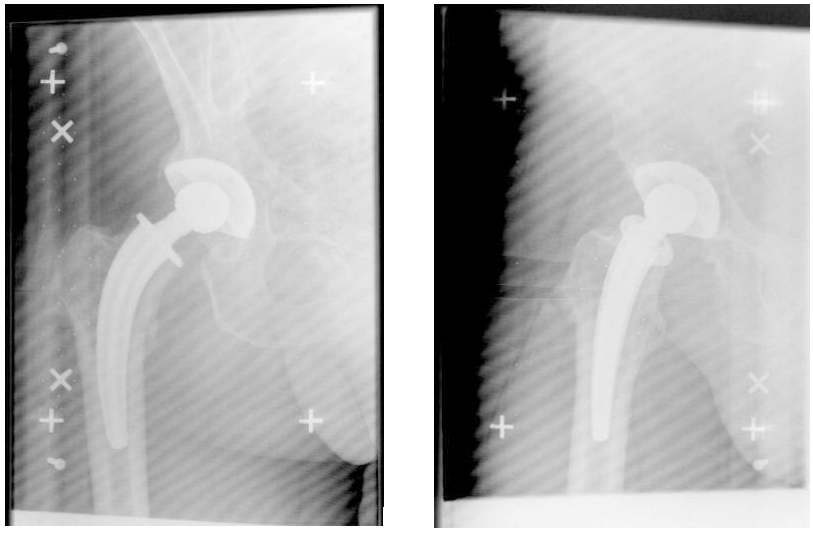


Figure 6. RSA images in 2 projections.

Positron emission tomography (PET)

PET is an advanced nuclear medicine technology established as a major research tool and an instrument in routine diagnostics. Areas in which PET is applied are, among others, oncology, where PET is used to diagnose cancer and monitor treatment response; cardiology, evaluating damage after heart attacks; and neurology, to diagnose neurological conditions [79, 115, 124]. Trace amounts of biologically relevant molecules labeled with radioactive isotopes (such as [18F] sodium fluoride) are administrated and detected by tomography. The resulting images demonstrate the regional concentration of radioactivity and can be converted to quantitative observations of the related biochemistry, measured as standardized uptake value (SUV). Combined with CT, this technique produces a 3-D image of the bone around the stem and the prosthesis cup. [18F] Fluoride PET (F-PET) images of periprosthetic bone can be analyzed with the use of a modification of the polar map software rendering volumes of interest (VOIs) [148] (figures 7 and 8).

F-PET correlates with bone blood flow and metabolic activity proportional to osteoblastic calcium uptake in the bone-forming process. With this technique, it is possible to observe ongoing metabolic activity related to bone formation. The application of F-PET in implant surgery has been minimal. The knowledge of the natural course of implant fixation according to F-PET is sparse, and the precision of the modified polar map method when applied to periprosthetic bone is unknown [147–149]. It is believed that fluoride isotope is taken up only by osteoblasts, reflecting osteoblastic activity and bone formation [141]. Although one experimental study suggests that even dead bone can show high activity, the role of passive diffusion and high affinity of [18F]

to HA remains uncertain [10]. No studies have evaluated the effects of denosumab in pBMD visualized with F-PET imaging of periprosthetic bone. Only one previous RCT had reported results from F-PET imaging of the skeleton in women with osteopenia who received teriparatide [47].

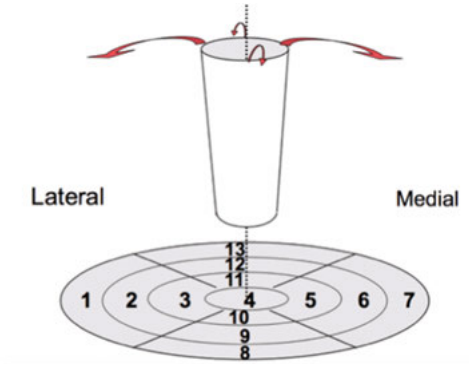


Figure 7a. The proximal femur is "flattened" to form a disc where sectors 1-7 correspond to Gruen zones 1-7. Additionally, there are 6 more sectors anterior and poste-rior to the implant. These sectors form the volumes of interest (Courtesy of Ullmark G.).

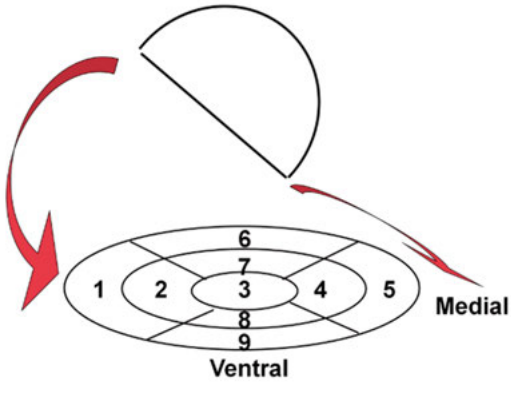


Figure 7b. The acetabulum is “flattened” to form a disc where sectors 1-5 correspond to Digas zones 1-5. Additionally, there are 4 more sectors anterior and posterior to the implant. These sectors form the volumes of interest (Courtesy of Ullmark G.).

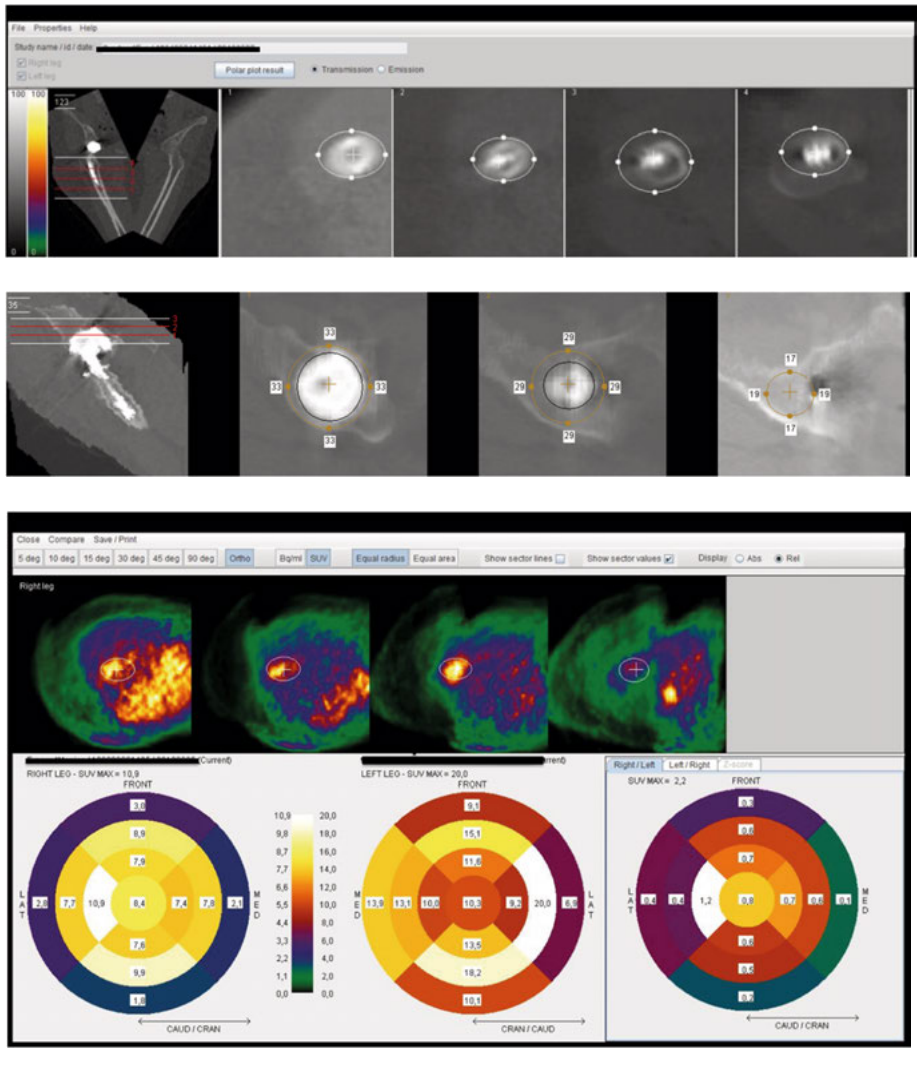


Figure 8. Modified Polar Map. CT images are used for the anatomic placing of VOIs. The results are shown as a colored map and in figures for each VOI.

Bone turnover markers (BTMs)

Bone turnover markers (BTMs) have proven useful scientific tools for monitoring bone formation and resorption [50]. They have been widely used for basic bone research, epidemiological and pharmaceutical studies and RCTs [12, 30, 51, 93, 105]. The BTMs have a circadian rhythm and could be affected by dietary intake. Thus, blood samples are being collected fasting in the morning.

Serum C-telopeptide of type 1 collagen (CTX, CrossLaps) is an often-used bone resorption marker and can be detected by radioimmunoassay technique. The breakdown products of type 1 collagen, the primary collagen in bone, are measured by CTX [125]. During bone resorption, type 1 collagen is degraded and releases CTX in the blood. Serum-Procollagen-1-N-Propeptid (S-P1NP) is a bone formation marker analyzed using an immunochemical electroluminescence technique. The levels of procollagen type 1, a precursor to collagen type 1, are measured by P1NP [125]. Procollagen type 1 is produced during bone formation, and P1NP is released in the blood.

Patient-reported outcomes measures (PROMs)

PROMs are frequently used as endpoints in clinical trials to report patients' symptoms, QoL and general experiences and preferences. Choosing the most appropriate PROM for a clinical study is essential to achieve trustworthy results. The improvements in pain and function after a THA are measured with instruments such as the Harris Hip Score (HHS). With high validity, this tool is the most commonly used instrument for assessing outcomes after a THA [59, 133, 138]. The EuroQol visual analogic scale (EQ-VAS) is a standardized non-disease-specific instrument for describing and valuing health-related QoL measures [119].

Open Questions

- Can denosumab prevent periprosthetic bone loss adjacent to the CFP stem?
- Can denosumab prevent periprosthetic bone loss adjacent to the Continuum cup?
- How will denosumab affect periprosthetic bone formation as measured by F-PET?
- Will the periprosthetic bone loss seen adjacent to the TOP cup continue at an 8-year follow-up? What is the implant survival rate?
- What is the precision of F-PET of bone around an uncemented cup?

Aims

Study I

The Denosumab and Total Arthroplasty (DATA) study was planned and accomplished as a Phase II randomized placebo-controlled clinical trial (RCT) primarily to investigate the effect of 2 subcutaneous injections of denosumab on femoral pBMD after an uncemented THA. The study's primary outcome was to investigate whether denosumab can prevent loss of pBMD in uncemented THAs with the CFP stem and performed as an EBM-level Ib study.

Secondary outcomes included investigating denosumab's effect on local and systemic bone turnover and clinical outcome.

Study II

A secondary outcome within the DATA study Clinical Trial Protocol was to investigate the effect of 2 subcutaneous denosumab injections on acetabular pBMD after an uncemented THA with the Continuum cup and performed as an EBM-level Ib study.

Also, secondary outcomes included in the DATA study were to investigate the effect of denosumab on local and systemic bone turnover and clinical outcome.

Study III

The study aimed to investigate changes in pBMD and implant survival for the TOP cup from a prospective cohort study with an 8-year follow-up and performed as an EBM-level IIb study.

Study IV

The study aimed to determine the inter- and intraobserver reliability, as well as the agreement and precision of analyzing periprosthetic SUV by F-PET around the uncemented Continuum cup.

Patients and methods

This thesis consists of three types of studies: one randomized, placebo-controlled clinical trial (RCT) (studies I and II), one prospective cohort study (study III) and one methodological study (study IV).

Ethical considerations

Studies were conducted according to good clinical practice (GCP) and applied to the Helsinki Declaration. Ethical approval was obtained for studies I-III from the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2011/297/2 and 2007/105/2). Studies I and II obtained an approval from the Swedish Radiation Safety Authority. Studies I and II were registered at ClinicalTrials.gov (2011-001481-18, NCT01630941). The DATA Clinical Study Report was delivered to The Swedish Medical Products Agency 2018.

The main ethical consoderation was the increased exposure to ionized irradiation from the F-PET investigations in studies I and II. In total, patients included in the full protocol were exposed to approximately 10 mSv, equivalent to 3 years of background irradiation. The patients without the PET/CT in the protocol were exposed to less than one week of additional background irradiation, which should be of minor or minimal concern. The increased exposure is most critical for young individuals, individuals in fertile age planning for reproduction and pregnant women, which were not included in the studies.

DXA-scanning is a routine procedure with the patient lying in a supine position on the scan table. In total the scan-time for lumbar spine and both hips is approximately 10 minutes and is painless just like an ordinary X-ray. The total irradiation dose from DXA was approximately 0.015mSv which corresponds to less than one week of background irradiation dose. Additional irradiation exposure by RSA was excluded from the DATA study protocol, due to irradiation dose concern.

Another consideration is the adverse reactions to the study drug denosumab in studies I and II. Local reactions to the injection, eczema and skin infections/cellulitis can been seen. Very rare adverse events such as hypocalcemi and osteonecrosis of the jaw have been reported.

Paper I and paper II

Study design of the DATA-study

The DATA study is a double-blind, randomized, placebo-controlled clinical trial (RCT) of denosumab. It is classified as EBM level Ib and involves a cohort of 64 patients undergoing uncemented THA with the CFP stem and the Continuum cup. Because denosumab was investigated for a new indication, it was conducted as a Phase II study under the supervision of the Swedish Medical Products Agency. Primary outcomes were changes in pBMD at Gruen zone 7 and the sum of Gruen zones 1-7 at 12 months, which are reported in paper I. Secondary outcomes were changes in pBMD around the cup at Digas zones 1-5 and the sum of Digas zones, which are reported in paper II. The total follow-up time was 24 months, and secondary outcomes also included DXA, BTMs and PROMs. Moreover, for half of the study population, secondary outcomes pSUV for Gruen zones 1-7 and the sum of 1-7 and pSUV for Digas zones 1-5 and the sum of 1-5 were evaluated by F-PET.

The collum femoris preserving (CFP) stem

The CFP stem (Waldemar Link GmbH & Co Hamburg, Germany) is an uncemented, short (range of length 82-135 mm, while other uncemented stems, e.g., Corail, have a range of length 130-190 mm), neck-preserving stem made of titanium alloy (Tilastan®) with a 70 µm microporous surface and a HA layer applied to the proximal 2 thirds (figure 9). It is designed for a subcapital osteotomy and a shape to ensure proximal fixation and load transfer to minimize proximal pBMD loss [118]. Despite these attributes, patients with the CFP stem show considerable proximal pBMD loss. In a prospective cohort study performed at our institution, there was a 31% pBMD decrease in Gruen zone 7 at 12 months [84]. Most of the changes in pBMD remained after 24 months. It remains unclear whether pBMD restitutes in the long-term perspective and, if not, whether implant stability is affected.

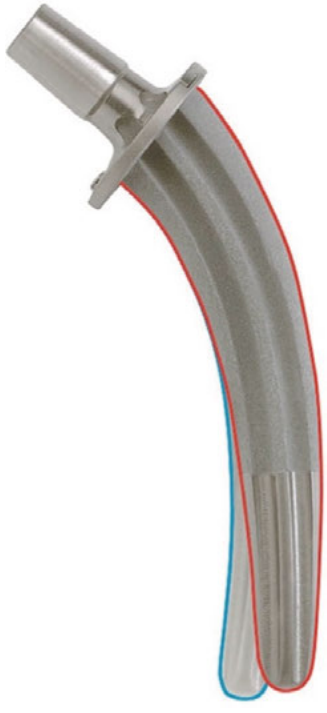


Figure 9. The CFP stem is available in 2 curvatures to accommodate individual patient anatomy. From Lazarinis et al., Acta Orthop 2013; 84(1): 32-39.

The Continuum cup

The Continuum® cup (Zimmer Co, Warsaw, IN, USA) is a press-fit hemispherical cup made of Tivanium®, a titanium alloy, to which a surface of Trabecular MetalTM, a highly porous biomaterial made from elemental Tantalum is bonded (Figure 10). The surface offers a high coefficient of friction and scratch fit that reduces micromotion and supposedly allows for rapid bone ingrowth. The Continuum shell used in the DATA study features a singular central hole (uni-hole), which is subsequently sealed with a screw once the handle instrument is removed. The Continuum® cup is fitted with a highly cross-linked PE elevated liner. To date, no studies have provided prospective findings on acetabular pBMD in relation to the Continuum cup.

Figure 10. The different types of Continuum cups ©Zimmer Biomet. In the DATA study, the uni-hole cup was used.

Study population of the DATA study

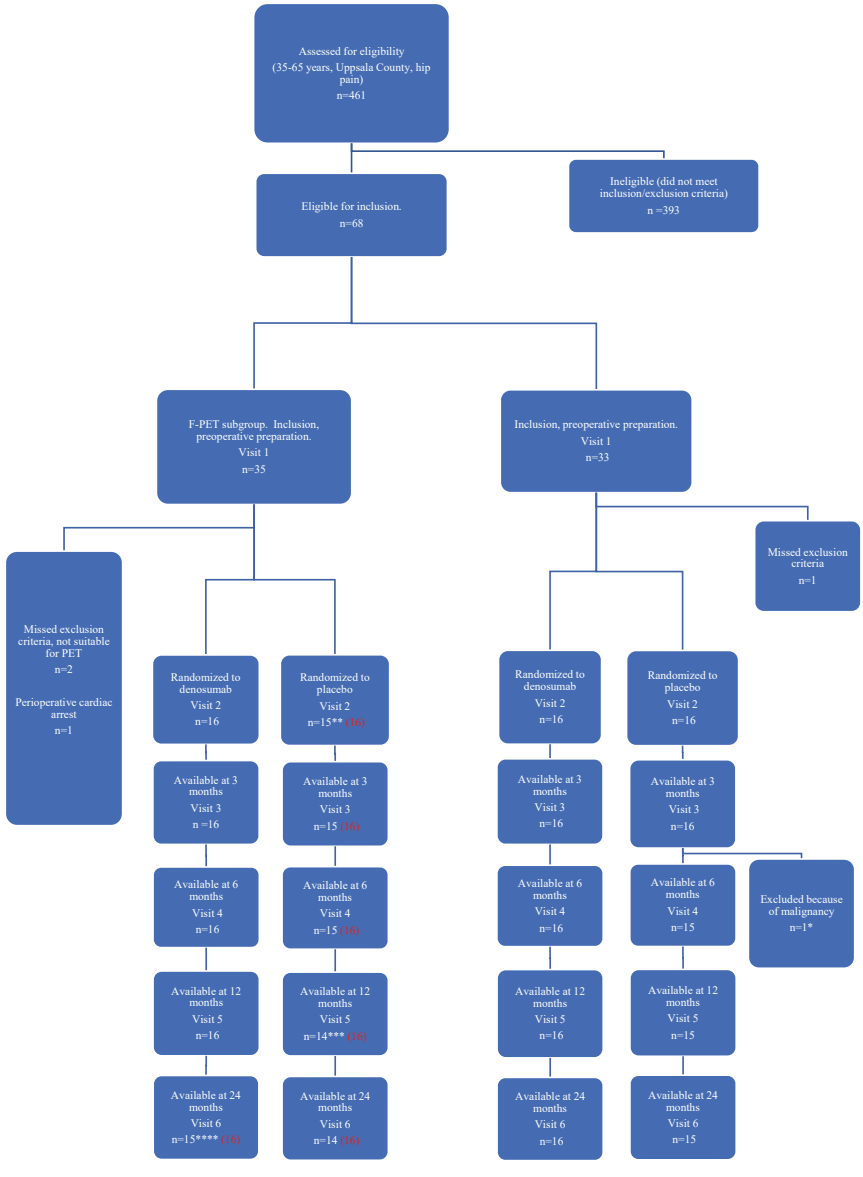
Patients were recruited from August 2012 to January 2015. All patients aged 35 to 65 years living in the Uppsala region and referred to the Department of Orthopedics, Uppsala University Hospital with unilateral OAH (Kellgren-Lawrence grade 3-4 for the affected hip and 0-1 for the unaffected hip) and having a body mass index (BMI) <35kg/m2 were eligible for inclusion [68]. Exclusion criteria were treatment with bisphosphonates, raloxifene, strontium, denosumab or parathyroid hormone in the 5 years preceding inclusion in the trial, systemic corticosteroid treatment for more than 3 months, malignant disease, an American Society of Anesthesiologist (ASA) score >3, alcohol or drug abuse, pregnancy, previous exposure to large irradiation doses, enrollment in other studies and any laboratory finding judging the patient to be unsuitable for the study. All participants gave oral and written consent to participate.

68 patients with unilateral OAH were enrolled in the study. 4 patients were excluded before randomization because of missed exclusion criteria at visit 1 (preoperative) (n=3) and perioperative complication (n=1). 64 patients (32 in the F-PET group) were randomized to treatment, but 1 patient in the placebo PET group did not receive the designated stem for technical reasons. Thus, 31 of 32 patients were eligible for analysis of femoral pSUV and 63 of 64 patients for femoral pBMD of the CFP stem, as reported in paper I. 1 patient was diagnosed with malignancy after visit 3 (3 months after surgery) and declined further participation in the study. 2 patients in the F-PET group (1 in the placebo and 1 in the denosumab group) were revised because of aseptic loosening

of the stem after visit 4 (6 months after surgery) and visit 5 (1 year after surgery) respectively. Thus, 61 patients were analyzed for the primary outcome at 12 months and are documented in paper I (figure 11).

Except for the patient diagnosed with malignancy after visit 3 and declining further participation, no other dropouts occurred regarding the secondary outcomes. Thus, 63 patients were analyzed for the secondary outcomes at 12 and 24 months, which are reported in study II (figure 11).

The baseline characteristics of the study population are shown in table 1.



* EQ-VAS, HHS and biomarkers at 6 months

** For technical reasons, one patient in the placebo group did not receive the designated stem

*** One patient in the placebo group was revised because of aseptic loosening of the stem

**** One patient in the denosumab group was revised because of aseptic loosening of the stem

Number of patients available for secondary outcomes differs in the F-PET subgroup and are shown in parenthesis

Figure 11. CONSORT Flowchart illustrating the enrollment and randomization process. Numbers represent patients available for analysis for the primary outcome. In parenthesis with red color, numbers represent patients available for analysis for the secondary outcome.

Table 1: Baseline characteristics of the study population

Table 1. Baseline (pre-op) characteristics of the study participants		
Characteristic	Denosumab (N=32)	Placebo (N=32)
Age (year) (Mean [SD])	58 (5)	59 (5)
Male (n [%])	12 (38)	13 (41)
Body mass index (kg/m^2) (Mean [SD])	27 (4)	27 (3)
Kellgren-Lawrence grading, unaffected hip (Median [Min, Max])	1 (0, 1)	1 (0, 1)
Kellgren-Lawrence grading affected hip (Median [Min, Max])	3 (3, 4)	3 (3, 4)
Harris Hip Score (Median [Min, Max])	58 (28, 81)	51 (33, 77)
CTX (ng/L) (Mean [SD]) N=31*	435.9 (192.0)	444.1 (184.2)
P1NP (µg/L) (Mean [SD]) N=31*	45.7 (16.2)	44.3 (14.7)
Z-score**, total hip (unaffected hip) (Mean [SD])	0.58 (1.13)	0.65 (0.67)
Z-score**, total hip (affected hip) (Mean [SD])	0.33 (1.20)	0.33 (0.91)
Z-score**, L1-L4 (Mean [SD])	0.91 (1.18)	0.83 (0.91)

* Because of incorrect handling, blood samples from one patient in the denosumab group were unavailable for analysis.

** Age- and sex-matched and weight-adjusted comparison to a White/Caucasian US reference population.

Methods

Dual-energy X-ray absorptiometry (DXA)

DXA of the affected hip, the contralateral hip and the lumbar spine was performed preoperatively, at 6, 12 and 24 months postoperatively using a Prodigy Advance® system (GE-Lunar, Madison, WI, USA). In addition, duplicate DXA hip implant scans of the affected hip were performed at 1-3 days and 3, 6, 12 and 24 months postoperatively. The pBMD in the 7 Gruen zones around the CFP stem, the sum of Gruen zones 1-7 and the 5 zones according to Digas around the cup, as well as the sum of Digas zones 1-5, were analyzed [38, 53]. The precision of the femoral DXA measurements in our institution with repeated scans after repositioning, expressed as the coefficient of variation (CV), is 1.1% for Gruen zone 4 and 5.7% for Gruen zone 7 [84]. The precision

of the periprosthetic acetabular DXA measurements is 2.99% for Digas zone 1 and 3.59% for Digas zone 3 [85].

[^{18}F] sodium fluoride positron emission tomography-CT (F-PET)

F-PET scans of the hips and lumbar spine were performed preoperatively and at 3 and 6 months postoperatively on the first 32 patients. Periprosthetic SUV was obtained by analyses of scans using a modified version of the PET visualization software Polar Map [11, 148]. In study I, 31 of 32 patients were analyzed for pSUV because 1 did not receive the designated stem. In study II, pSUV was analyzed for all 32 patients. Seven regions of interest (ROIs) roughly corresponding to the 7 Gruen zones (study I) and 5 ROIs corresponding to the 5 Digas zones (study II), as well as the sum of Gruen zones 1-7 and the sum of Digas zones 1-5, were analyzed.

Bone turnover markers (BTMs)

Morning fasting blood samples were drawn 7-14 days before surgery, 1-3 days postoperatively and 3, 6, 12 and 24 months postoperatively. Serum was prepared and analyzed for CTX – CrossLaps, as a marker of bone resorption and P1NP, as a marker of bone formation. The CV analysis at our laboratory, certified in accordance with the international standard ISO 15189:201, was 6% for CTX - CrossLaps and 3% for P1NP.

Patient-reported outcome measures (PROMs)

The HHS and the EQ-VAS were recorded 7-14 days preoperatively and 3, 6, 12 and 24 months postoperatively.

Conventional radiography

Conventional digitized AP and lateral hip and AP pelvic radiographs were obtained before surgery. The degree of OAH was classified in both hips according to the Kellgren and Lawrence system [68]. AP pelvic, lateral and AP hip radiographs were obtained 1-3 days and 12 months postoperatively.

Drug administration

The study drug was administered 1-3 days and 6 months postoperatively by one of 2 independent nurses after blood was drawn for BTMs, after DXA scanning and, for half of the patients, after F-PET. Randomization was performed in blocks of four. Blinding was assured by asking the patient to look away during preparation and subcutaneous injection of either 60 mg of denosumab or 1 ml of saline.

Statistical analysis

Based on the 30% pBMD loss in Gruen zone 7 found in a previous study [84], the power analysis showed that 58 patients would be sufficient to detect a

halved reduction of BMD in the denosumab group at 12 months. To compensate for dropouts, 64 patients were randomized.

We relied on support from the Uppsala Clinical Research Center for the statistical analysis. Analyses were performed using SAS software, version 9.4 (SAS Institute). Standard descriptive statistics were used to compare baseline characteristics.

Continuous variables were summarized using means with standard deviations or as medians with minimum-maximum ranges, as appropriate. Categorical variables were expressed as frequencies and percentages. Efficacy analyses were carried out using analysis of covariance (ANCOVA) models. Treatment contrasts were expressed as model-based geometric mean ratios (with 95% confidence intervals [CIs]). For the HHS, a non-parametric ANCOVA was used. Analyses were made according to the intention-to-treat principle. Because of the study's exploratory nature, no further adjustments for multiple comparisons were undertaken.

Paper III

Study III is an 8-year follow-up of a previous prospective study on the uncemented TOP cup [85]. The original study's outcomes were pBMD measured with DXA and implant stability by RSA. The follow-up time was 24 months.

The current study extended the follow-up of the TOP cup by investigating 8-year implant survival and pBMD as measured by DXA. Clinical results were assessed with the HHS.

The trabeculae-oriented pattern (TOP) cup

The TOP® cup is a press-fit hemispherical cup of titanium alloy (Tilastan®). The shell has a 70 µm microporous surface and a 20 µm thick brushite coating, a low-calcium precursor to HA. It was developed to minimize acetabular periprosthetic bone loss with a segmental row of threads around the equator to ensure stable anchorage in the acetabulum (figure 12). The TOP cup is designed with a mediocaudal recess to provide a wider range of motion in adduction and prevent impingement from the neck of the stem. The liners are constructed of ultra-high-molecular-weight polyethylene (UHMWPE). The shell has holes covered with polyethylene plugs for additional screw fixation when needed. However, the holes were not used and no screws were inserted.

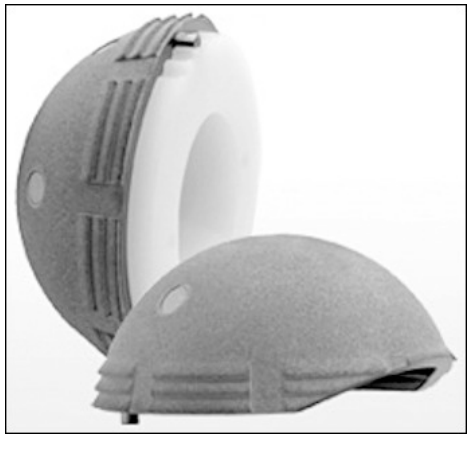


Figure 12. The trabeculae-oriented pattern, TOP cup © Waldemar Link.

Study population

30 patients with primary OAH eligible for uncemented THA were included in the original study. The inclusion criteria were symptomatic, radiographically confirmed OAH, age between 20 and 65 years and body weight under 100 kg.

Exclusion criteria included inflammatory conditions (e.g., rheumatoid arthritis) diagnosed based on American Rheumatism Association (ARA) criteria, systemic glucocorticoid use, other disabling musculoskeletal disorders not involving the hip, malignancy, alcohol or drug dependence, psychiatric conditions, chronic infectious diseases and osteoporosis as identified by DXA. 1 patient was excluded from further follow-up due to revision surgery resulting from an early deep infection. Consequently, the final cohort included 29 patients with primary OAH.

In the present study, all 29 patients were invited to participate in a follow-up (on average 8.6 years after surgery) investigation with clinical examination, radiology and pBMD measurement with DXA. Exclusion criteria for the clinical follow-up were cup revision surgery or death, whichever occurred first. All patients were investigated with DXA, HHS and X-rays.

At 8 years of follow-up, 5 patients underwent revision surgery of the cup. They were therefore not eligible for clinical follow-up. 2 patients refused to participate but reported no implant-related problems after telephone contact (figure 13). Thus, 23 patients (12 women) with a mean age of 64 (range 55-73) years and a median BMI of 26 (20-31) participated in the clinical follow-up.

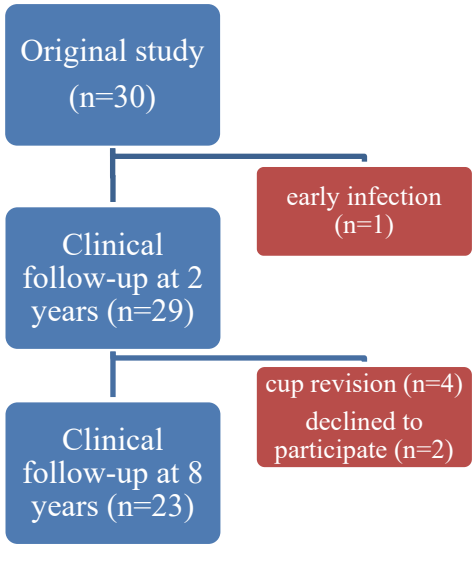


Figure 13. Flowchart of the 8-year clinical follow-up.

Dual-energy X-ray absorptiometry (DXA)

DXA scans of the operated hip were performed using the same system as in the original study: Prodigy Advance System (GE-Lunar, Madison, WI, USA). The pBMD in the 5 zones was analyzed according to Digas [38].

Clinical outcome measures and radiology

The HHS was used to assess patient-reported outcomes of hip function. AP and lateral radiographs of the hip and a standard pelvic view were obtained to examine possible implant loosening and PE wear.

Radiostereometric analysis

The original study describes the tantalum marking of implants and bone perioperatively [85]. Mean errors (MEs) of the rigid body fittings and conditional numbers (CNs) were calculated.

Statistics

All variables were summarized using standard descriptive statistics. The within-subjects effect was calculated using repeated measures ANOVA. Mauchly's test determined the assumption of sphericity. If sphericity was violated, the Greenhouse-Geisser correction was applied. The significance level was set at 0.05 and 95% CIs were calculated. Implant survival was estimated using Kaplan-Meier (KM) analysis. All statistical calculations were performed using SPSS Statistics version 27 (IBM Corp, Armonk, NY, USA).

Paper IV

Study IV is a methodological study examining inter- and intraobserver reliability, agreement and precision of F-PET around the uncemented Continuum cup.

Study population

All F-PET images of the hip with implants from the 3-month follow-up of the DATA study on the uncemented Continuum cup were eligible. Images from 32 patients (19 women) with a mean age of 58 ± 5 years and a mean BMI of 26 ± 4 were included.

[^{18}F] sodium fluoride positron emission tomography-CT (F-PET)

Periprosthetic SUV was obtained by analyses of scans using a modified version of the PET visualization software Polar Map, known as "quantification of hip prosthesis (QHPR)" [11, 148].

2 independent observers analyzed the F-PET investigations from the 3-month follow-up and re-analyzed the same investigations after a minimum of 3 weeks. The observers were orthopedic surgeons without experience in F-

PET analysis. Before the previous study, the observers received a 4-hour training session from an experienced QHPR software user. The analysis includes three manual steps: 1) alignment of the longitudinal axis of the cup with the Y-axis in 2 planes so that the acetabulum is horizontally aligned (figure 14a), 2) positioning of the limits of the VOIs along the longitudinal axis and 3) placing the circumference of the VOIs in each slice in the horizontal plane based on anatomic landmarks and extension of the implant (figure 14b). These steps render nine VOIs in which the software calculates a mean SUV (figure 14c). We separately analyzed the mean SUV of every VOI, the sum of VOIs 1-5 and the sum of VOIs 1-9. We also analyzed the mean SUV of a total VOI consisting of VOIs 1-5 merged and a total VOI comprising all VOIs (VOIs 1-9 merged). VOIs 1-5 in the coronal plane closely relate to the 5 zones of Digas and the sum of Digas 1-5.

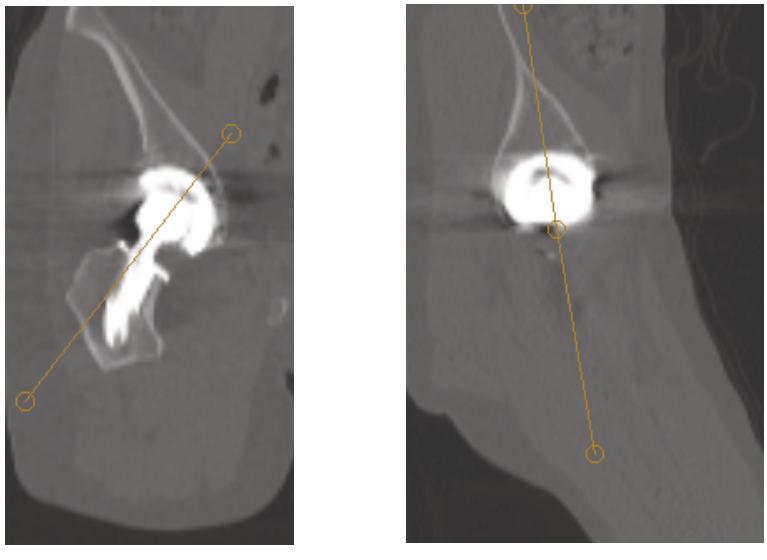


Figure 14a. F-PET analysis. The acetabulum is aligned horizontally in 2 projections.

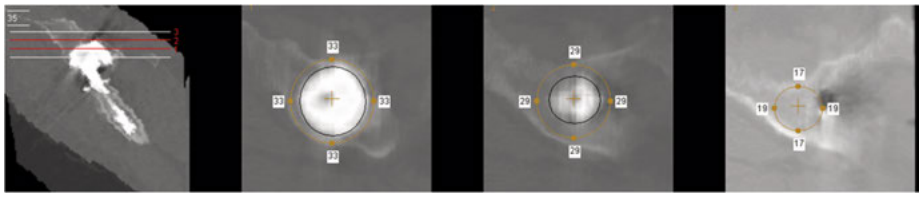
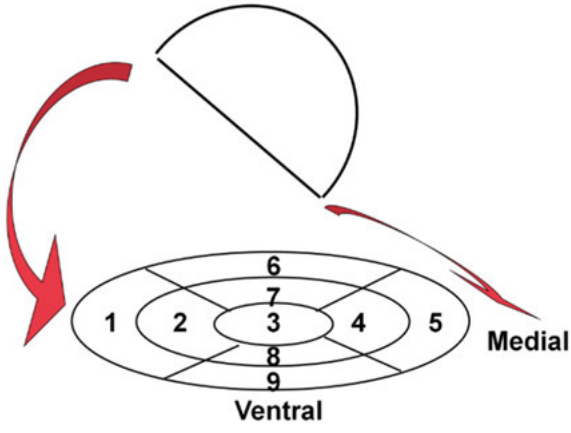


Figure 14b. F-PET analysis. Volumes of interest (VOIs) are first placed parallel to the horizontally aligned acetabulum in the AP view. VOIs are then outlined in the horizontal plane. Figures around the ellipses in the image to the right show the distance to the ellipse's center and function as support in placing the VOIs. An inner ellipse is placed around the cup to exclude this from the analysis.



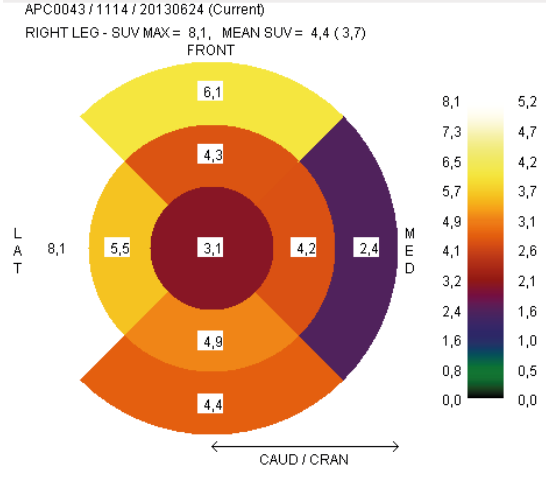


Figure 14c. F-PET analysis. Mean standardized uptake values of the right acetabulum are folded out to form a circle with sectors (VOIs), where the circles 1-5 correspond to Digas zones 1-5, and VOIs 6-7 and 8-9 are placed posterior and ventral of the cup, respectively.

Statistics

All analyses were performed using SPSS software version 28.0.1.0 (142) (IBM).

Variables were summarized as means and standard deviation. We determined the inter- and intraclass correlation coefficient (ICC) reliability with 95% CI) using a 2-way, mixed-effects, single-measures model with absolute agreement. An ICC <0.50 was considered poor, 0.50-0.75 moderate, 0.75-0.90 good and >0.9 excellent [78].

Inter-rater agreement was determined using Bland-Altman plots. We performed a one-sample t-test for inter- and intra-rater differences based on 0 difference as the null hypothesis and with the significance level set at $p<0.05$. We then plotted the difference between each pair against the mean value.

Precision was defined as the degree to which repeated measures produced the same value under unchanged conditions. To establish a level of precision, we determined the coefficient of variation (CV%) for each VOI for the 2 observers and observer 1 versus observer 2. The CV% is the standard deviation of all differences between the 2 measurements divided by the mean value for all measurements multiplied by 100.

The first measurements for each observer were used to analyze the interobservers' reliability, agreement and precision.

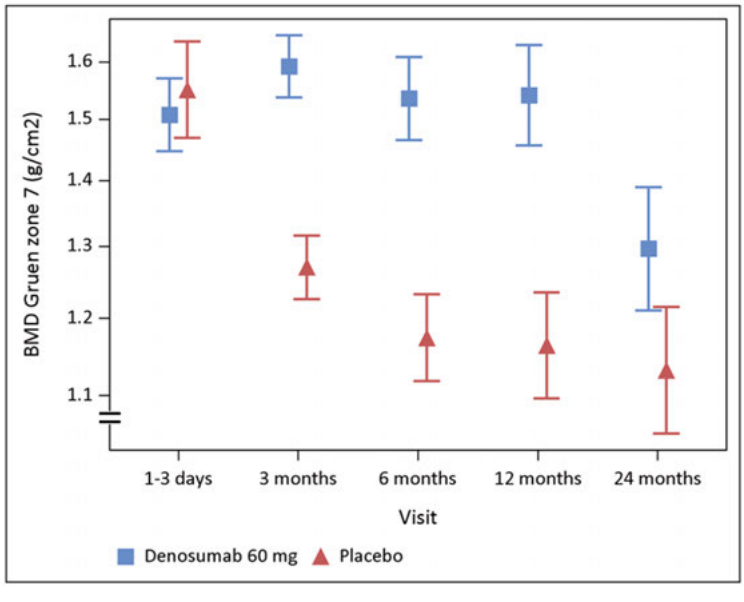
Results

Paper I

Periprosthetic bone mineral Density (pBMD)

Primary outcome: At 12 months, pBMD in the denosumab group showed minimal change compared to baseline. pBMD in Gruen zone 7 was 32% (95% CI 22-44) higher and the sum of pBMDs in Gruen zones 1-7 was 11% (95% CI 8-15) higher compared to the placebo group at 12 months.

Secondary outcomes: At 24 months, the difference between the groups, though still present, had decreased. pBMD in Gruen zone 7 was 15% (95% CI 4-27) higher in the denosumab group than in the placebo group and 4% (95% CI 0-8) higher in the sum of Gruen zones 1-7 (figure 15).



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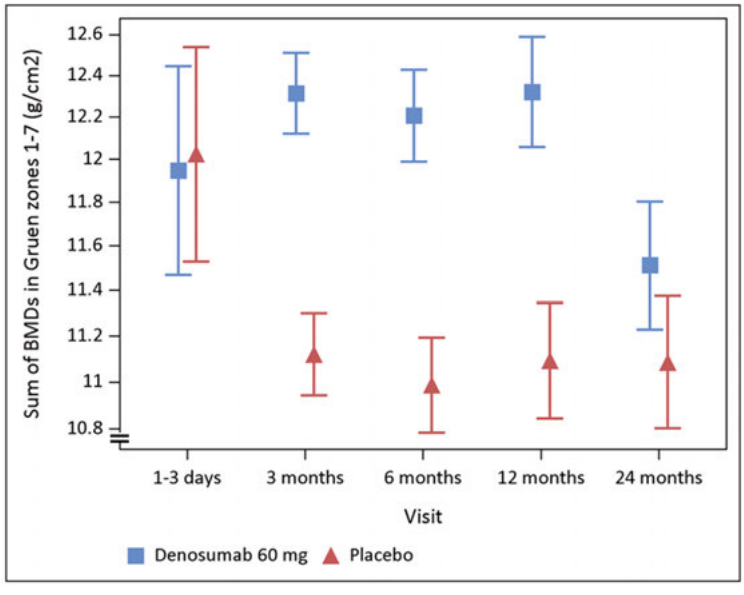


Figure 15: pBMD in Gruen zone 7 and the sum of pBMDs in Gruen zone 1-7. The Y-axis is truncated for better visualization. Descriptive geometric means with confidence intervals are provided for pre-randomization visits. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1-3 days and at 6 months postoperatively.

Periprosthetic standardized uptake value (pSUV)

Secondary outcomes: In both the denosumab and the placebo groups, pSUV for the sum of Gruen zones 1-7 was higher at 3 and 6 months compared to baseline. At 3 months, pSUV for Gruen zone 7 was 32% (95% CI 1-53) lower and the sum of pSUVs in Gruen zones 1-7 was 37% (95% CI 18-51) lower than in the placebo group (figure 16). After 6 months, there was no between-group difference.

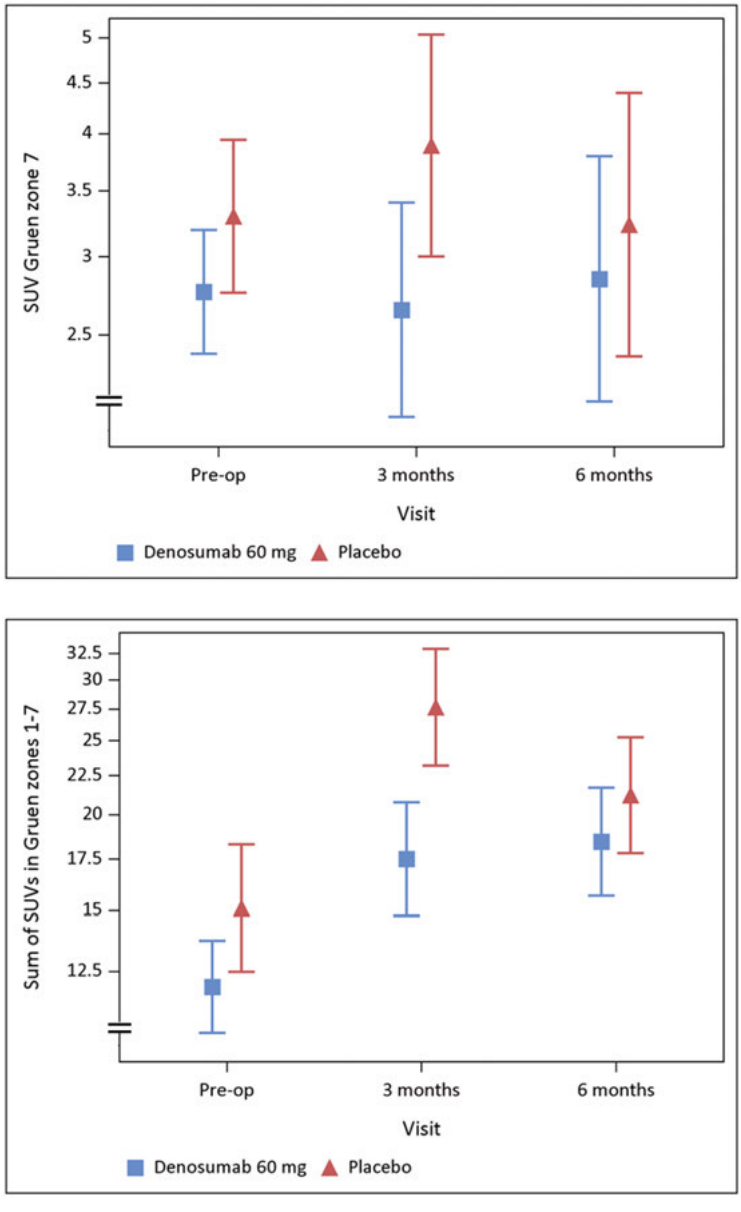


Figure 16: pSUV in Gruen zone 7 and the sum of pSUVs in Gruen zones 1-7. The Y-axis is truncated for better visualization. Descriptive geometric means with confidence intervals are provided for pre-randomization visits. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1-3 days and at 6 months postoperatively.

Bone turnover markers

Secondary outcomes: Blood concentrations of bone resorption and formation markers were pronouncedly reduced in patients treated with denosumab after 3, 6 and 12 months (figure 17). However, after 24 months, both marker levels were above baseline levels.

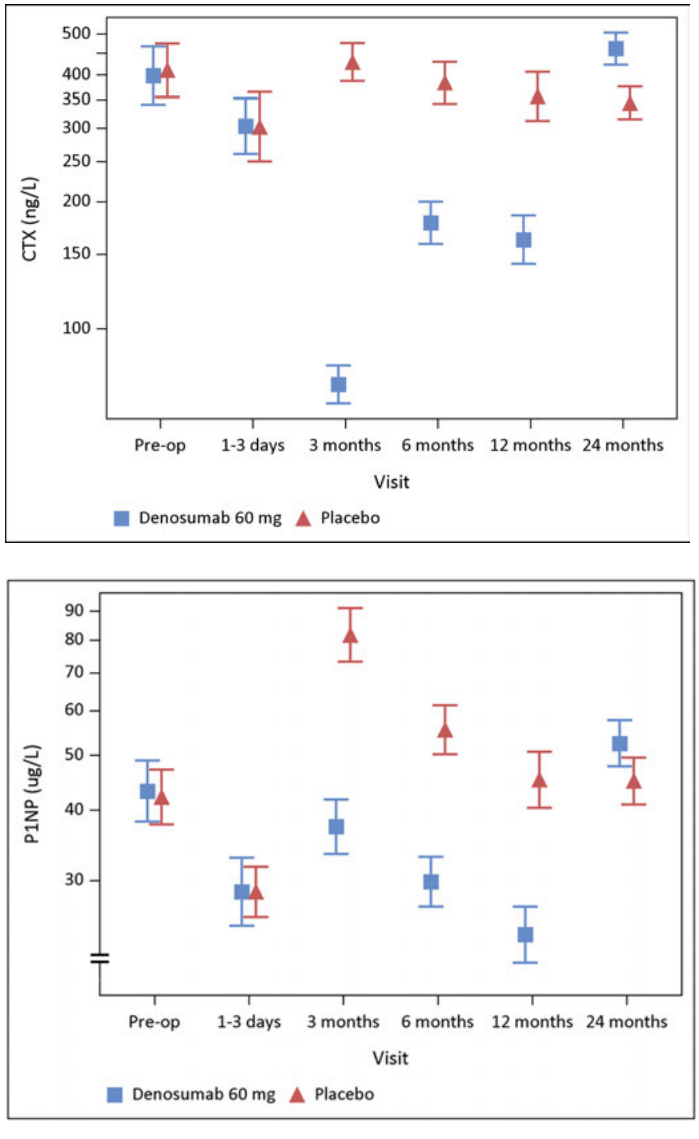


Figure 17: Serum CTX and serum P1NP. The Y-axis is truncated for better visualization. For visits pre-randomization, descriptive geometric means with confidence intervals are given. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1-3 days and at 6 months postoperatively.

Patient-reported outcome measures and adverse events (AEs)

Secondary outcomes: There was no difference between groups in EQ-VAS at any time point. The placebo-treated patients had slightly higher HHS after 12 months than those treated with denosumab (100 vs. 94). After 24 months, there was no between-group difference.

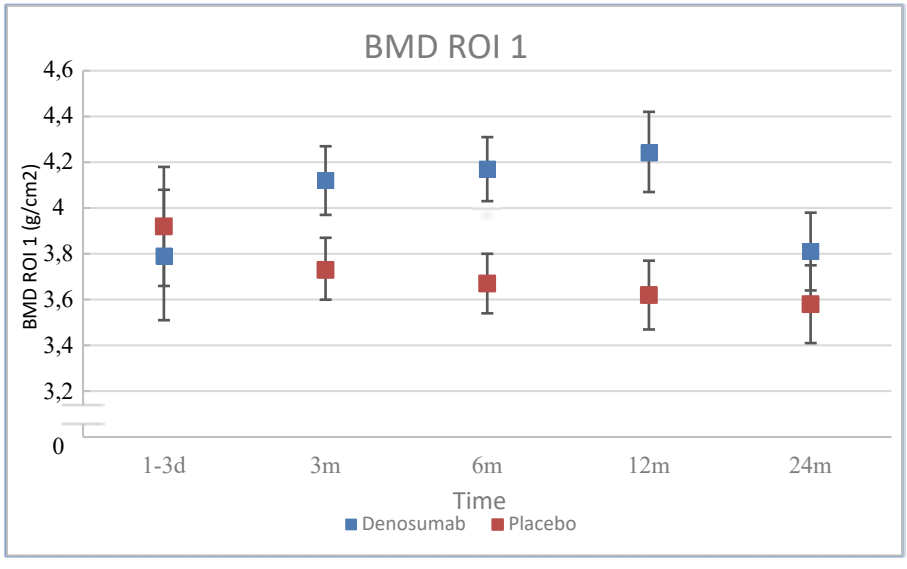
During the study, the frequency of adverse events (AEs) and serious adverse events (SAEs) was lower in the denosumab group. None of the events were considered probably related to the denosumab (see supplementary appendix). 2 patients (one from each group) underwent revision surgery because of aseptic stem loosening during the study period.

Paper II

Periprosthetic bone mineral density (pBMD)

Secondary outcomes: Denosumab-treated patients had 10% higher pBMD (CI 1.1-1.2) in ROI 1 than placebo-treated patients after 3 months and 17% (CI 1.1-1.2) higher pBMD after 12 months (figure 18). Similar increases were seen in the denosumab group compared to placebo-treated patients in ROI 2, ROI 3, ROI 4 and the sum of ROIs 1-5 up to 12 months after surgery (figure 18 and supplementary appendix).

After 24 months, the effect on pBMD for patients treated with denosumab declined. However, it was still statistically significantly higher in ROI 2 and the sum of ROIs 1-5 compared to patients treated with placebo.



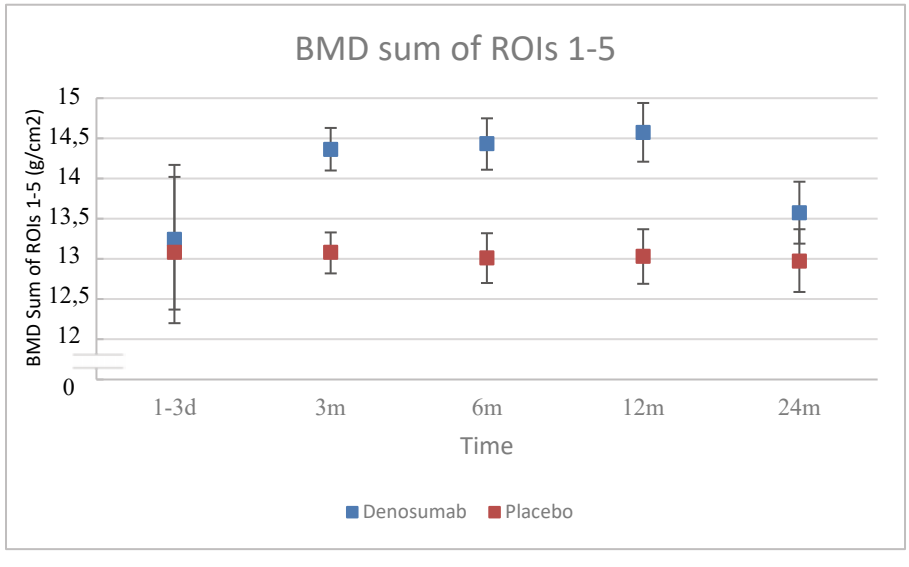


Figure 18. Periprosthetic BMD in ROI 1 and the sum of ROIs 1-5. The *y-axis* is truncated for better visualization. Descriptive geometric means with 95% confidence intervals are given for pre-randomization visits. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1 to 3 days and at 6 months postoperatively.

Periprosthetic standardized uptake value (pSUV)

Secondary outcomes: Patients treated with denosumab had reduced acetabular pSUV across all ROIs, including the sum of ROIs 1-5, after 3 and 6 months compared to patients who received placebo. However, the reduction in pSUV, varying from -21% to -34%, was statistically significant only after 6 months in ROI 1, ROI 2, ROI 3, ROI 4 and the sum of ROIs 1-5 (figure 19).

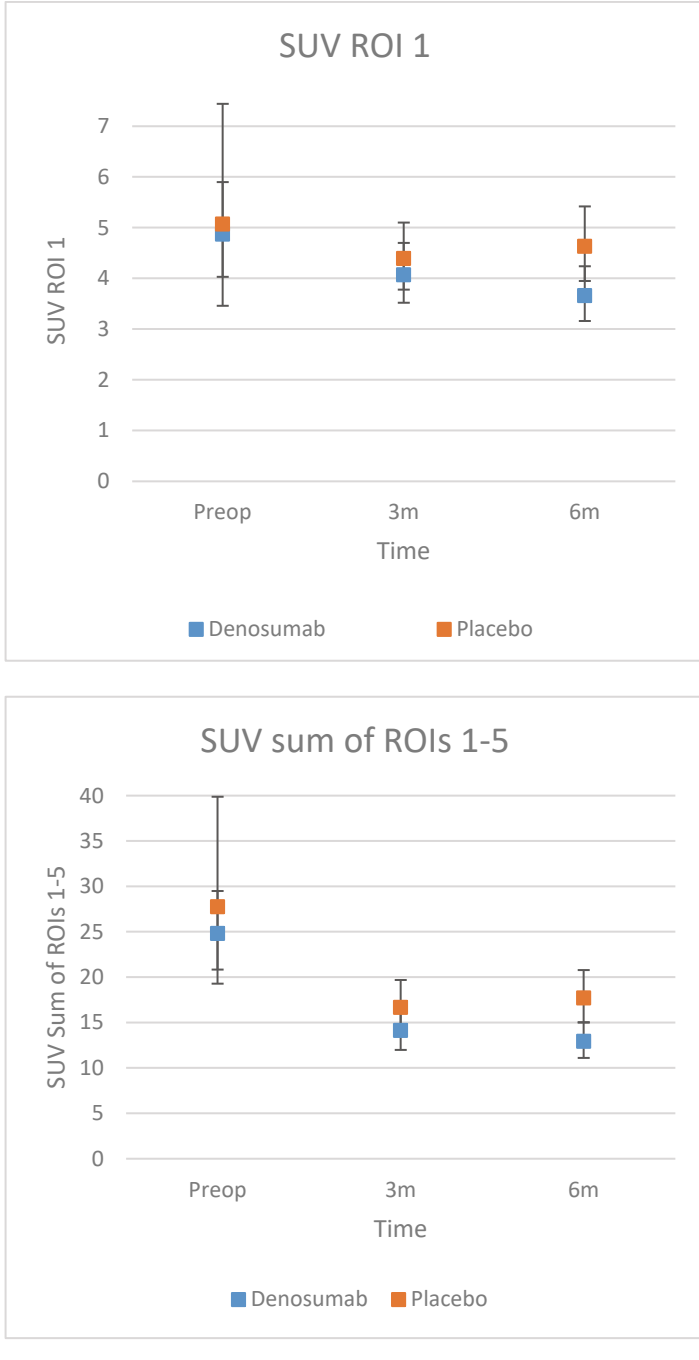


Figure 19. Periprosthetic SUV in ROI 1 and the sum of ROIs 1-5. The *y*-axis is truncated for better visualization. Descriptive geometric means with 95% confidence intervals are given for pre-randomization visits. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1 to 3 days and at 6 months postoperatively.

Bone turnover markers

Secondary outcomes: 3 months after surgery, CTX was 83% (95% CI 80-85) lower in the denosumab group and remained suppressed at 6 and 12 months, as described in paper I. Between 12 and 24 months after surgery, CTX increased and was higher in the denosumab group at 24 months. P1NP serum levels followed the same pattern, with an initial decrease followed by an increase between 12 and 24 months in the denosumab group, as described in paper I.

Patient-reported outcome measures and adverse events

Secondary outcomes: HHS was slightly lower in the denosumab group after 12 months, as outlined in paper I. After 24 months, there was no between-group difference.

As described in paper I, AEs and SAEs were distributed among the 2 groups.

Paper III

Implant survival and revision

As reported in the original study, 1 patient underwent revision because of an early deep infection 3 months after surgery. 3 patients had undergone isolated cup revision and 1 total hip revision (both cup and stem) during 2 to 8 years of follow-up. Thus, we found an 8-year cup survival rate for all reasons of 83% (CI: 70-97) (figure 20). When revision due to aseptic loosening of the cup was the endpoint in the KM analysis, the implant survival rate was 86% (CI: 74-99) (figure 21).

A review of patients' surgery journals revealed macroscopically significant PE liner wear in 2 of 4 patients who had undergone revision due to cup loosening.

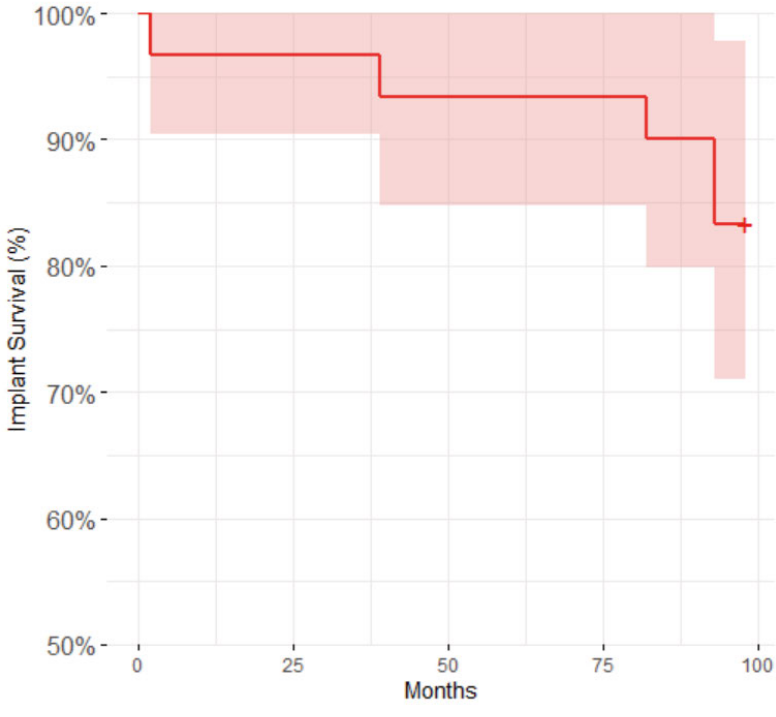


Figure 20. Kaplan-Meier survival curve for TOP cup with cup revision for all reasons as an endpoint. The x-axis (time) is described in months.

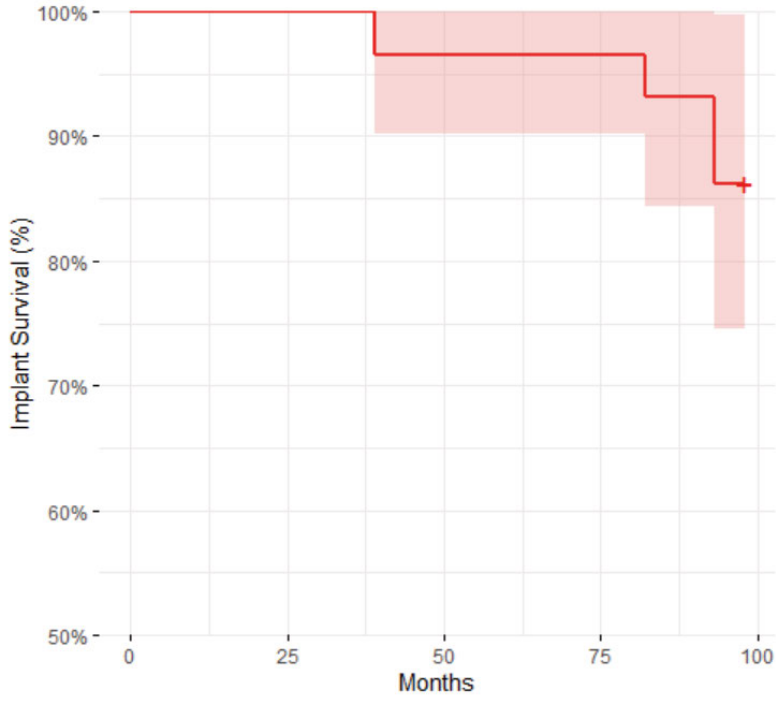


Figure 21. Kaplan-Meier survival curve for TOP cup with cup revision for aseptic loosening as an endpoint. The x-axis (time) is described in months.

Dual-energy X-ray absorptiometry

We found a continuous decrease of 12% (CI: 5-17) of pBMD in Digas zone 1 (p=0.005) and a reduction of 12% (CI: 7-17) in Digas zone 2 (p=0.003) 2-8 years after surgery. A smaller, statistically non-significant decrease in pBMD (5%, CI: 2-12) was also seen in Digas zone 3 (medially). In Digas zone 4 (ramus superior) and 5 (the ischial tuberosity), continuous non-significant increases in pBMD of 8% (CI: -7-21) and 10% (CI: 2-18), respectively, were recorded (figure 22).

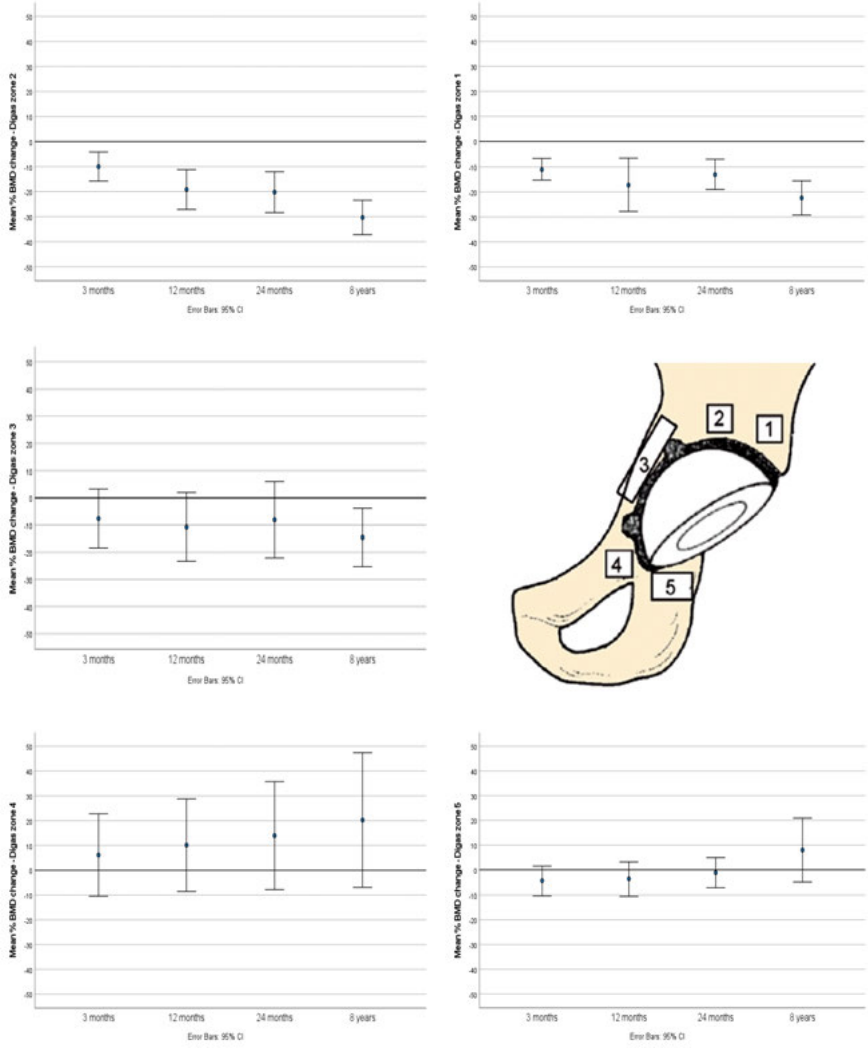


Figure 22. Changes in pBMD from baseline in Digas zones 1-5 (n = 21). Error bars represent 95% confidence intervals.

Clinical outcome measures and radiography

Clinical outcome at the 8-year follow-up was excellent, with a mean HHS of 95 (77-100). 22 of 23 plain digital AP radiographs of the pelvis were assessable. No signs of cup loosening were observed in any patient, but migration of the hip head was seen in 8 hips (figures 23a and 23b).

Figure 23a. Radiography of a stable cup at eight years (right). Direct postoperative image to the left.

Figure 23b. Radiography of a cup with PE wear at eight years (right.) Direct postoperative image to the left.

Radiostereometric analysis

For technical reasons, only 9 patients were eligible for RSA measurements at the 8-year follow-up. 1 patient had a mean error (ME) above the acceptable range of 0.3 (0.7), leaving 8 patients available for evaluation. We found a mean cranial translation of 0.39 mm (CI: 0.14 – 0.64) and a mean anterior tilt of 0.73° (CI: -0.49 – 1.95) at 8 years (table 2 and figure 24).

Table 2: Migration of the TOP cup at 8 years compared to baseline and 2 years, as measured with radiostereometric analysis (8 patients).

		Cup migration 0 - 8 years		Cup migration 2 - 8 years	
	N	Mean (95% CI)	Range	Mean (95% CI)	Range
X-translation (mm) medial+/lateral-	8	-0.07 (-0.24 – 0.1)	-0.27 – 0.39	-0.09 (-0.17 to -0.01)	-0.23 – 0.03
Y-translation (mm) proximal+/distal-	8	0.39 (0.14 – 0.64)	0.01 – 0.78	0.09 (0.01 – 0.16)	-0.03 – 0.22
Z-translation (mm) anterior+/posterior-	8	0.26 (0.13 – 0.39)	0.06 – 0.41	0.13 (-0.01 – 0.26)	-0.09 – 0.34
X-rotation (°) anterior tilt+/posterior tilt-	8	0.73 (-0.49 – 1.95)	-1.57 – 3.32	0.25 (0.02 – 0.48)	-0.18 – 0.79
Y-rotation (°) retroversion+/anteversion-	8	0.78 (-0.10 – 1.66)	-0.54 – 2.21	0.38 (-0.09 – 0.84)	-0.03 –1.53
Z-rotation (°) increased+/decreased-inclination	8	-0.17 (-0.83 – 0.49)	-1.15 – 0.83	0 (-0.31 – 0.31)	-0.42 – 0.5

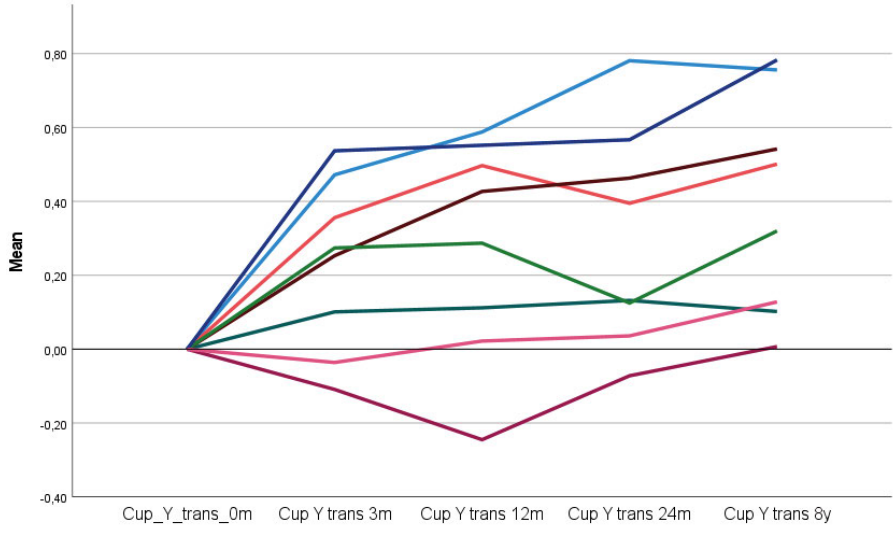


Figure 24: Translation of the cup along the y-axis up to 8 years at different time points (n=8).

Paper IV

Study IV demonstrates that quantitative analysis of periprosthetic F-PET uptake around an uncemented acetabular cup is reliable, exhibiting strong inter-rater agreement, moderate to good precision and the absence of proportional bias.

Intraclass Correlation Coefficient

The ICC for interobserver reliability ranged from 0.64 (CI: 0.00-0.84) to 0.91 (CI: 0.83-0.96). The lowest values were noted for VOIs 7, 8 and 9 and the highest for VOIs 5 and 6. The ICC for intraobserver reliability for observer 1 ranged from 0.72 (CI: 0.47-0.85) to 0.94 (CI: 0.88-0.97), with the lowest values for VOIs 8 and 9. For observer 2, the ICC ranged from 0.82 (CI: 0.6-0.92) to 0.93 (CI: 0.86-0.96), with high values in all VOIs. The lowest values for observer 2 were noted for VOIs 4 and 7 (table 3).

Table 3: Intraclass correlation coefficients (ICCs) with 95% confidence intervals (95% CIs) for intra- and interobserver reliability of periprosthetic [18 F]-fluoride PET for each VOI and the entire periprosthetic volume (sum of VOI 1-9 and merged VOI 1-9).

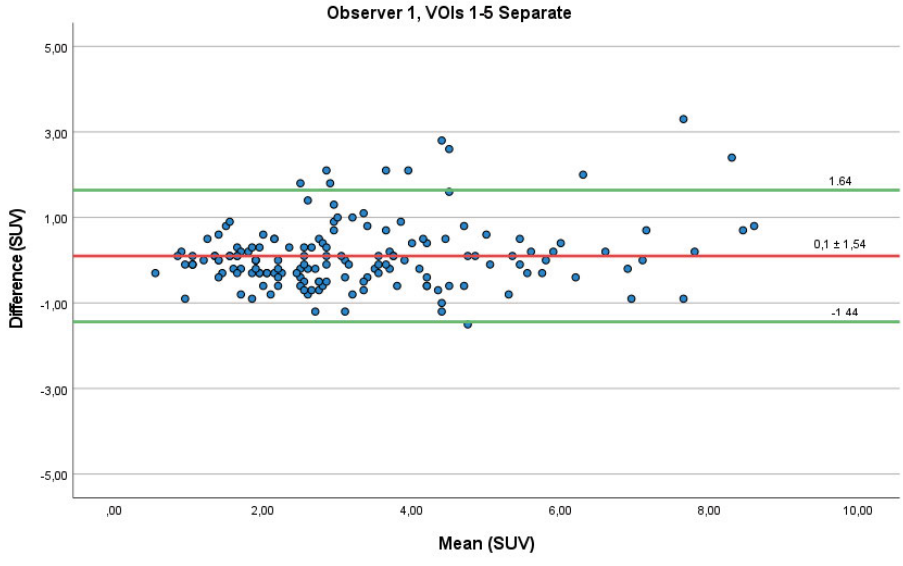
	Observer I		Observer II		Observer I vs Observer II	
	ICC	95% CI	ICC	95% CI	ICC	95% CI
VOI 1	0.8	0.48-0.92	0.87	0.75-0.93	0.74	0.53-0.87
VOI 2	0.89	0.79-0.94	0.86	0.71-0.93	0.8	0.63-0.9
VOI 3	0.92	0.83-0.96	0.87	0.75-0.93	0.8	0.36-0.92
VOI 4	0.86	0.73-0.93	0.82	0.6-0.92	0.8	0.61-0.9
VOI 5	0.91	0.82-0.96	0.92	0.85-0.96	0.91	0.83-0.96
VOI 6	0.83	0.67-0.92	0.93	0.86-0.96	0.91	0.82-0.95
VOI 7	0.82	0.66-0.91	0.84	0.67-0.92	0.64	0.004-0.86
VOI 8	0.74	0.53-0.86	0.89	0.79-0.95	0.7	0.47-0.84
VOI 9	0.72	0.47-0.85	0.93	0.87-0.97	0.66	0.39-0.82
VOI 1-9	0.87	0.83-0.89	0.9	0.87-0.92	0.81	0.77-0.85
VOI 1-9 Merged	0.94	0.88-0.97	0.9	0.8-0.95	0.85	0.41-0.94
VOI 1-5	0.9	0.87-0.93	0.89	0.85-0.92	0.85	0.8-0.89
VOI 1-5 Merged	0.92	0.85-0.96	0.89	0.79-0.94	0.83	0.46-0.93

There were statistically significant differences in interobservers' mean SUV but only for the sum of VOIs 1-9 and the merged VOI 1-9. These differences, however, were small, ranging from -0.13 (CI: -0.24 to -0.01) to -0.42 (CI: -0.59 to -0.25) with narrow limits of agreement. No statistically significant difference between observers was noted for the sum of VOIs 1-5 and the merged VOI 1-5. For intraobservers' mean SUV, there was a statistically significant difference for both observers for the sum of VOIs 1-9, with a range from 0.11 (CI: 0.01-0.21) to -0.18 (CI: -0.27 to -0.09) but not for the merged VOI 1-9. The sum of VOIs 1-5 showed a statistically significant difference for observer 2.

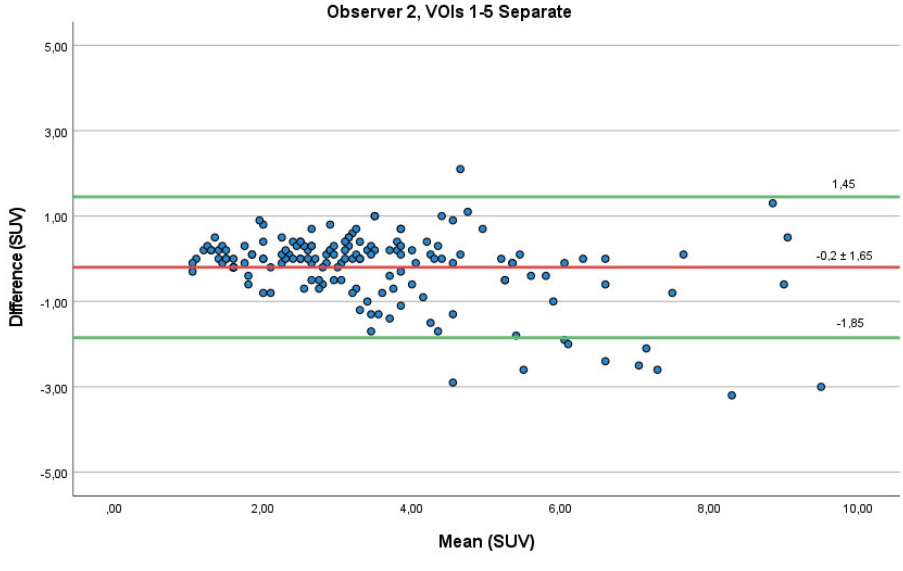
Bland-Altman plots

Bland-Altman plots showed no evidence of proportional bias, as the difference between measurements did not change with increasing SUVs (figure 25).

A)


Observer 1, VOIs 1-5 Separate
Difference (SUV)
Mean (SUV)
1.64
0,1 ± 1,54
-1.44
5,00
3,00
1,00
-1,00
-3,00
-5,00
,00
2,00
4,00
6,00
8,00
10,00

B)


Observer 2, VOIs 1-5 Separate
Difference (SUV)
Mean (SUV)
1.45
-0,2 ± 1.65
-1.85
5,00
3,00
1,00
-1,00
-3,00
-5,00
,00
2,00
4,00
6,00
8,00
10,00

C)

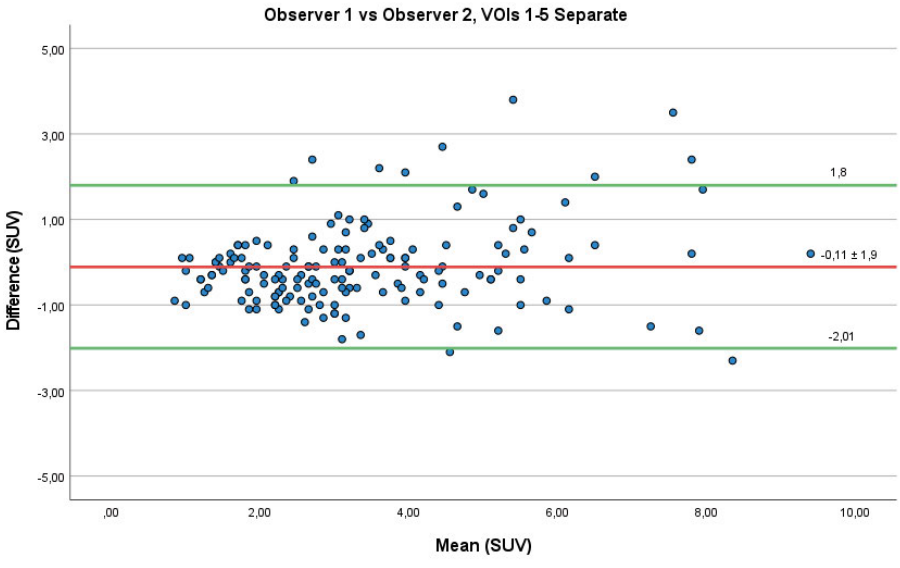


Figure 25 a-c. Bland-Altman plot for observer 1 (A), observer 2 (B) and observer 1 vs. 2 (C) for volumes of interest (VOIs) 1-5 separately. Each dot represents a mean SUV difference, with 32 (patients) x 5 (VOIs) dots. The Y-axis represents the difference in standardized uptake value (SUV) between observers and the X-axis depicts the mean SUV for double measurements. The red line represents the mean difference with a 95% confidence interval. Green lines denote the 95% limit of the agreement interval.

CV

The interobserver CVs% ranged from 15.9-40.9. The CVs% for observer 1 ranged from 13.9-39.1 and for observer 2 from 16.3-29.8 (table 4).

Table 4: Precision for volumes of interest (VOIs) for each volume for the sum of VOIs 1 to 9 and 1-5 separately and the VOI 1-9 merged and VOI 1-5 merged for each observer and between observers expressed as coefficients of variation (CVs%).

					CV %								
Examiner	VOI 1	VOI 2	VOI 3	VOI 4	VOI 5	VOI 6	VOI 7	VOI 8	VOI 9	VOI 1-9	VOI 1-9 Merged	VOI 1-5	VOI 1-5 Merged
I	21,5	19,8	19,2	27,9	24,8	27,2	26,3	39,1	29,4	27,1	13,9	24	16,5
II	22,1	20,8	19,2	29,8	25,8	18,5	19,1	23	19,9	22,7	16,3	23,8	16,9
I vs II	27,7	26,9	21,9	30,7	24,2	20,9	27	40,9	35,3	31,2	15,9	28,7	18,5

Discussion

The primary endpoint for the DATA study shows that 2 doses of denosumab prevent loss of pBMD for the uncemented CFP stem after 12 months, but the effect diminishes after 24 months. Investigated as a secondary endpoint, denosumab prevents loss of pBMD for the uncemented Continuum cup, but comparable to the results for the CFP stem, the effect diminished after 24 months.

The long-term survival rate for the TOP cup is inferior to retrospective studies with the same implant and inferior to the survival rates from other uncemented acetabular implants. Moreover, periprosthetic bone loss continues at 8 years, but the clinical implications remain to be determined in future studies.

Our findings show that periprosthetic F-PET analysis can be reliably performed with strong agreement and moderate precision using QHPR software. The main objective of research studies should be to validate this method across various implant types and accurately evaluate the images following patient repositioning. Future research should determine how SUV values predict implant complications after THA.

Paper I

The main finding of this study is that denosumab inhibits pBMD loss around the stem 12 months after uncemented THA. Still, the effect decreases upon cessation with an observed rebound effect on BTMs and a rapid decrease in BMD the first year after discontinuation.

Denosumab reduces early implant migration in cemented total knee arthroplasty (TKA) [86]. However, no effect on stem subsidence was recorded in an RCT by Aro et al. that investigated the effect of 2 doses of denosumab in older women operated with an uncemented THA [5]. They found a reduction in BMD loss around the stem in the denosumab group, similar to what we observed in our study [4]. We investigated the effect of denosumab on a cohort of younger patients who are more likely to receive uncemented implants and are projected to have the implants for several decades. This means that a potential decrease in the risk of revision because of pBMD loss will benefit this group of patients the most. One more non-randomized, prospective study has confirmed the BMD-sparing effect of denosumab in uncemented femoral

stems [103]. Thus, in addition to results from multiple clinical osteoporosis trials, the study by Aro et al. provides further support for the external validity of the DATA study results.

In our study, we found a substantial rebound effect with a steep increase in BTMs and loss of pBMD 1 year after discontinuation of denosumab. Despite the population dissimilarity between our study and Aro et al.'s, our findings align regarding the rebound effect observed in BTM curves.

This rebound phenomenon upon cessation of denosumab was not well described when planning the present study. It has since been reported in numerous studies where denosumab was given for several years and implies a potential risk for unfavorable biomechanical properties [14, 94]. This effect could be the reason for the reported increase in the risk of spontaneous vertebral fractures following discontinuation of denosumab [2, 6, 29]. In the abovementioned studies on femoral pBMD [5, 103], denosumab was given only twice and the follow-up was 2 years or less.

The findings from the F-PET analysis in our study suggest that pSUV is indicative of the rate of bone formation in this particular context. Levels of P1NP decreased following the decrease of CTX, thus indicating a total bone turnover reduction. Still, a shift towards bone formation occurred because pBMD was preserved in the denosumab group. Furthermore, at the time of most marked suppression (3 months) the reduction of pSUV in the denosumab group compared to placebo was most pronounced. The decrease in P1NP is likely caused by a coupling mechanism between resorption and formation, implying that the body strives to achieve a balance in bone metabolism [14].

Strengths of the DATA study include the RCT design with blinding of all investigators and patients, careful selection of patients with unilateral OAH according to strict inclusion and exclusion criteria and meticulous follow-up according to case report forms with a minimal number of patients lost to follow-up. These strengths ensure high internal validity. It is the only RCT on denosumab and THA that, apart from DXA, includes F-PET and BTMs. The combination of these modalities makes it possible to investigate the outcome in terms of pBMD and the biological events of the bone during the process. In addition, the study was conducted autonomously and devoid of any support or influence from the pharmaceutical industry, as stated above.

There are several limitations of our study. The external validity of our findings could be questioned as only a small proportion of patients assessed for eligibility met the criteria. However, in the study by Aro et al., similar effects on pBMD were reported despite differences in patient age, implant design and timing of the first denosumab injection [5]. This finding supports the external validity of our study [5]. The primary outcome we focus on, periprosthetic pBMD, is in essence a surrogate measure. The question is whether denosumab can lower the risk of revision because of implant loosening or periprosthetic fractures. However, studying these rare events requires a different methodology, such as registry studies. Performing F-PET on the entire study cohort

would have yielded more robust results; however, we opted to examine only half of the cohort because of financial constraints and irradiation reasons. RSA could have provided useful information on early migration, but its execution was hindered because of technical limitations and concerns regarding radiation exposure.

Our findings suggest that 2 doses of denosumab preserve pBMD in uncemented THA only for the period with rapid postoperative loss of pBMD. Nevertheless, the resilience of the effect diminishes once denosumab's effect subsides. To achieve a lasting impact, prolonged treatment with denosumab or additional treatment with other antiresorptives should be considered to maintain pBMD. More studies on the long-term effects of pBMD loss are needed to establish to what extent this constitutes an actual clinical problem and identify patients at risk before commencing prophylactic treatment with antiresorptives.

Paper II

The main findings derived from this study are that 2 doses of denosumab effectively prevent the loss of acetabular pBMD after an uncemented THA during the first year. However, similar to femoral pBMD, the effect on acetabular pBMD decreases after 2 years. Moreover, consistent with the reduction in femoral pSUV, denosumab also reduced acetabular pSUV [109].

2 doses of denosumab prevented loss of acetabular pBMD compared to placebo and increased acetabular pBMD compared to baseline. Previous studies have reported a reduction in acetabular pBMD in the proximal and central periacetabular ROI and an increase in pBMD in the distal ROI during the 1st year following the insertion of an uncemented THA cup [36, 85, 100, 122]. To date, only one RCT has evaluated the impact of antiresorptive treatment on acetabular pBMD after a THA. A single intravenous administration of pamidronate was reported to reduce acetabular pBMD loss after 26 weeks. However this effect was no longer observed after a period of 2 years [159, 160]. No RCT has previously been published on the effects of denosumab on acetabular pBMD. The effect of 2 doses of denosumab on acetabular pBMD in the present study is consistent with previous reports of femoral pBMD [5, 101, 109].

Few RCTs have investigated bone metabolism using F-PET; however, in one RCT, bone formation was stimulated for 12 weeks with daily subcutaneous teriparatide injections in older women with osteopenia. That RCT reported increases in BTMs and lumbar spine BMD (but not proximal femur), and increased osteoblastic activity in the lumbar spine, pelvis and proximal femur by F-PET [47]. In contrast, we found reduced BTMs and acetabular pSUV but increased pBMD in denosumab-treated patients.

The reduced pSUV in patients treated with denosumab compared to placebo, observed in both acetabular and femoral periprosthetic bone at 3 and 6 months, is likely attributable to the biological effect of the initial dose of denosumab. This effect is characterized by depressed osteoclast activity and an insufficient coupling to osteoblast activity, as evidenced by the systemically decreased levels of CTX and P1NP [109]. An experimental study suggests that the uptake of [18F] NaF and the associated increase in SUV may result from mechanisms beyond osteoblastic activity, such as the affinity of [18F] NaF to hydroxyapatite [10]. However, studies on necrotic bone following resurfacing hip arthroplasty show reduced uptake in F-PET corresponding to areas of necrotic bone [153, 152, 154].

No data have been published on the effect of denosumab on cup stability assessed by RSA. For technical reasons, we did not include RSA in our study protocol. However, the absence of cup revisions during the 2-year study period suggests that denosumab does not negatively impact the initial stability of an uncemented cup.

Compared to baseline, we observed a decrease in acetabular pSUV for patients treated with both placebo and denosumab, which contrasts with the increased levels of femoral pSUV reported in study I. A possible explanation for the differences in postoperative pSUV findings between the acetabulum and proximal femur may be that the acetabulum, located in the proximal part of the hip joint, is close to bone affected by OAH. In contrast, the femoral head, also affected by OAH as the distal part of the hip joint, is resected and replaced during surgery [150, 151]. Consequently, only the extra-articular regions of the proximal femur remained available for pSUV investigation after THA. In contrast, the acetabular component of the THA was positioned directly onto the previously affected subchondral bone.

Our study observed significantly reduced CTX levels after 3 months, followed by sustained suppression at 6 and 12 months, and similarly decreased bone formation marker P1NP levels. These results are consistent with findings from large osteoporosis studies on denosumab [30]. Following the discontinuation of denosumab treatment, a rebound phenomenon was noted, characterized by elevated levels of bone resorption and formation markers rising above baseline levels, as documented in osteoporosis studies [145].

The primary strength of the DATA study is that it represents the first RCT incorporating a pharmaceutical drug in the study protocol to assess its impact on acetabular pBMD and pSUV following THA. The study is characterized by stringent inclusion and exclusion criteria, well-defined radiological diagnosis of OAH, standardized surgical techniques, consistent use of implants and postoperative care. Additionally, the careful administration of case report forms, external monitoring and a minimal patient attrition rate enhanced our study's internal validity. Moreover, the study was conducted as an independent academic investigation without any support from the pharmaceutical industry.

Our study also has some limitations. The study's sample size was based on a power analysis for the primary outcome, femoral pBMD and not acetabular pBMD, 1 year after the initial dose of denosumab or placebo. The secondary outcomes reported were prespecified and followed according to the clinical trial protocol. However, while these outcomes provide valuable and potentially explanatory information, they should be interpreted cautiously.

The transferability of our findings to other implants (both uncemented and cemented), age groups, anatomical sites or diagnoses is not readily evident. This study is the first RCT to report on the effects of denosumab on acetabular pBMD and only one previous RCT reported the effects of a single intravenous dose of pamidronate [159, 160]. Consequently, the external validity of our results is limited.

Additionally, the significance of acetabular pBMD as a surrogate variable for implant loosening and poor clinical outcomes remains to be determined.

A similiar positive effect on pBMD during 1-year antiresorptive treatment with BPs has been observed on femoral pBMD [5, 101]. Unfortunately, the effect was not sustainable. If prevention of pBMD loss is demanded, treatment with antiresorptive agents, whether denosumab or BPs, should be extentded for a longer time. At present, it is unknown how long that period should be.

Paper III

The original study found excellent short-term results, good primary stability and pBMD loss in the proximal zones around the TOP cup. The main findings in the present 8-year follow-up study of the TOP cup are:

- TOP cup shows an inferior cup survival rate compared to other uncemented cups and
- pBMD around this uncemented cup did not recover after 2 years but continued to decrease in the proximal zones.

In the original study, the TOP cup presented an excellent survival rate of 97% at 2 years. In this prospective study, 29 patients were followed for 8 years, and 4 had undergone cup revision surgery because of aseptic loosening. The overall survival rate of the cup at 8 years (4 patients revised due to aseptic loosening and 1 patient due to infection) was reduced to 83%. When the endpoint was limited to aseptic loosening of the cup, the survival rate was reduced from 100% at 2 years to 86% at 8 years. 2 studies on the TOP cup report excellent outcomes, demonstrating 100% survivorship at 7 years [17, 107]. A recent retrospective study by Mosconi et al. involving 662 TOP cups, with a mean follow-up of 12 years, demonstrated an overall survival rate of 91%, with aseptic loosening being the primary cause of revision [99]. Despite the longer follow-up period, the improved survival rate relative to our findings may be

attributed to ceramic femoral heads, UHMWPE liners and the advanced generation of high cross-linked PE liners in their study cohort. The use of the metal head in conjunction with non-cross-linked PE can result in significant liner wear, as evidenced in 2 of the 4 cases revised in our study, ultimately leading to aseptic cup loosening. Mosconi et al. found that a substantial proportion of patients (22%) were lost to follow-up, introducing uncertainty regarding the reported survival rates and raising the possibility that poorer outcomes may be present among those lost to follow-up compared to those who completed the study.

Our hypothesis that poor-quality PE liners contribute to significant liner wear, periprosthetic osteolysis and subsequent aseptic cup loosening is contested by the early loosening theory [96]. This theory posits that implant loosening may begin during or immediately after surgery due to inadequate interlocking between the bone and implant or due to compromised bone quality. Micromovements of the implant generate elevated fluid pressure at the bone-implant interface, triggering periprosthetic osteolysis through a cascade of inflammatory responses.

Mid-term results from retrospective, single-center, multicenter and registry studies on various uncemented acetabular implants have demonstrated survival rates exceeding 94% after more than 6 years of follow-up [61, 71, 74]. The 15 μm thick HA coating on the TOP cup was intended to promote bone ingrowth, facilitate bony gap filling and enhance secondary implant stability. However, this type of coating does not prevent bone demineralization around uncemented cups and may contribute to third-body wear, negatively impacting the long-term stability of the cup [82].

The original study documented a significant reduction of proximal pBMD around the TOP cup after 2 years. Our current study observed a similar long-term steady reduction of pBMD in the proximal zones around the implant. These findings are consistent with other studies on pBMD in uncemented cups [75, 98, 121]. A similar decline in pBMD in the proximal zones was reported around the uncemented Continuum cup as described in study II [75] and in a prospective study on the uncemented Trilogy®-cup by Digas et al. [36], where the pBMD was measured using DXA. 2 prospective studies on uncemented cups corroborate our findings, showing a sustained decrease in pBMD at 2 and 5 years post-surgery [9, 121]. In contrast, Field et al. reported preservation of pBMD in the proximal zones 2 years after surgery [42].

According to Wolff's law, increased pBMD in the proximal zones might be anticipated due to increased load and bone remodeling. However, research has shown that rigid fixation of a press-fit cup transmits forces sideways to the periphery [97, 163], resulting in stress shielding and leading to osteolysis around the uncemented cups. Although the clinical significance of proximal pBMD loss remains uncertain, the proximal regions around the uncemented cups are frequently the site for osteolytic lesions and are a major cause for revision surgery after THA [112].

Our follow-up study also demonstrates excellent clinical outcomes (HHS=95), albeit slightly less favorable compared to the original study (HHS=99), which is expected in this mid-term 8-year post-operative follow-up. This difference did not surpass the minimal clinically important difference [133] and is consistent with other mid-term studies on the TOP cup, which report HHS scores ranging from 87 to 96 [17, 99, 107].

In the original 2-year follow-up study, X-rays showed no evidence of cup or head migration. However, in our cross-sectional analysis of AP pelvic radiography from this 8-year follow-up, head migration in 8 hips was observed, suggesting potential PE liner wear. The development of periprosthetic osteolysis is significantly influenced by the biological response to wear debris from the PE liner, which partly depends on particle size and concentration as determined by the PE wear rate [49]. Notably, the surgeons reported substantial PE wear in 2 of our patients who underwent cup revision. Incorporating a non-cross-linked PE liner in our study and the observed head migration in the 8 non-revised hips indicate poor liner quality.

The strengths of our study include its prospective design, the complete follow-up of all patients concerning implant survival and extensive 8-year clinical assessments using DXA and X-rays. To our knowledge, no other prospective studies have been conducted on the TOP cup during such an extended follow-up period. Furthermore, we are unaware of any other research on uncemented cups that includes long-term DXA follow-up for pBMD.

Our study has several limitations. First, the sample size is relatively small, with only 23 patients available for clinical follow-up. Nevertheless, this remains the only study on an uncemented cup with an extended follow-up that includes high-accuracy DXA measurements of pBMD. Second, the use of the HHS for clinical assessment is a limitation. The ceiling effects of the HHS are well-documented and alternative tools might offer more sensitive measures for evaluating patients after a primary THA. However, we used the same scoring method in the original study for comparative purposes. In the 2-year follow-up, the stability of the cup was investigated using RSA. Unfortunately, technical limitations restricted RSA to only 8 patients at the 8-year follow-up, which is insufficient to draw definitive conclusions regarding the cup's 8-year stability. The literature frequently notes challenges in detecting the tantalum markers placed in PE liners of the cups, which often results in a significant loss of patients to follow-up [37, 162]. Nevertheless, we analyzed RSA on the remaining 8 patients, revealing a mean cranial translation of 0.39 mm and a mean anterior tilt of 0.73° at 8 years. In comparison, one RCT evaluating 2 uncemented cups reported mean proximal translations of 0.05 mm and 0.25 mm at 5 years [8]. Another RCT on an uncemented dual mobility cup observed a proximal translation of 0.21 mm at 6 years [64]. However, plain radiography did not reveal any indications of cup migration, despite the limitations of this technique in contrast to RSA. In the future, developing CT-based imaging

technologies, such as CT-based micromotion analysis, may address the current technical limitations associated with RSA [111]. Regrettably, RSA analysis could not be conducted at the 2- and 8-year follow-ups for the 4 patients with aseptic loosening. Consequently, RSA could not elucidate the cause of cup loosening in these cases. The original study used specific inclusion criteria, which may limit the generalizability of the results to other patient populations. On the other hand, in clinical praxis, most patients undergoing uncemented hip arthroplasty are similar to those included in our study.

In summary, inferior survival rates at the 8-year follow-up were seen in the TOP cup. Moreover, pBMD in the proximal zones continues to decline 8 years after surgery, suggesting that this particular uncemented cup is ineffective in preventing periprosthetic bone loss.

Paper IV

Study IV shows that quantitative analysis of periprosthetic F-PET uptake around an uncemented acetabular cup is reliable, with good interrater agreement, moderate to good precision and no proportional bias.

F-PET is an effective, non-invasive method for quantifying bone formation in any skeleton site, including the periprosthetic bone. The analysis and reporting of periprosthetic F-PET have been demonstrated in several ways. Some studies on periprosthetic F-PET have used max SUV instead of mean SUV and manually positioned VOIs [23, 76, 80]. The observers in these studies classified the uptake patterns and concluded that F-PET shows significant promise in differentiating diagnoses between septic and aseptic loosening. However, the reliability and agreement of F-PET between observers were not reported.

Other studies have used mean SUV to quantify F-PET and standardized VOIs, which differ from QHPR [140, 149]. Ullmark et al. applied F-PET to evaluate the activity of impacted bone grafts, and Son et al. attempted to establish a reference for the postoperative F-PET uptake on periprosthetic bone at different time points after surgery. Both studies employed VOIs corresponding to the Gruen zones of the femur [53]. Son et al. used VOIs based on the DeLee and Charnley zones for the acetabulum [33]. However, the significance of reference material will be limited without a universally recognized protocol for the analysis and reporting of periprosthetic F-PET.

Following its introduction by Ullmark et al. in 2013 [148], QHPR has been extensively employed in multiple studies investigating periprosthetic F-PET [146, 150, 151]. One study reported ICCs from 0.86 to 0.95 [109]. However, we found no other study documenting periprosthetic F-PET's reliability, agreement or precision.

Our study proposes a standardized methodology for analyzing quantitative, periprosthetic F-PET around acetabular THA components. A standardized method is critical for comparing studies and establishing SUV thresholds for septic and aseptic loosening diagnostics.

The prevailing belief suggests that F-PET findings indicate bone formation. Nevertheless, a cautious approach is warranted when interpreting the biological implications of F-PET in bone. According to one experimental report, the uptake of [18F] and the increased SUV could potentially be explained by mechanisms such as the affinity of [18F] to hydroxyapatite rather than the activity of osteoblast [10]. However, the credibility of this hypothesis is being questioned in light of findings from a randomized clinical trial investigating the impact of denosumab on periprosthetic bone [75], as well as other relevant studies [3, 144].

The strengths of this study include the pre-specified study protocol, the inclusion of observers with minimal previous experience in PET analysis and the consistent and standardized approach to data analysis.

Our study also has weaknesses. Using only 2 observers could weaken the external validity of the study. Furthermore, the lack of an established minimal clinically important difference for periprosthetic F-PET [62] prevented us from performing a power analysis to ascertain the requisite number of patients and observers. On the other hand, we analyzed all available patients scanned with F-PET in our previously described RCT without excluding any measurements [75].

This study's findings do not allow for any conclusions to be made about the periprosthetic F-PET method due to the absence of patient repositioning and rescanning. However, we can make inferences regarding the image analysis's reliability, precision, and agreement. Our study only included 1 type of acetabular cup, and the results could potentially differ between different cup designs, such as screw cups versus press-fit cups or cemented versus uncemented cups. The F-PET images were analyzed consecutively and not randomly, potentially affecting the results. However, we believe that the large case volume and a ≥3-week interval between analyses have hindered the observers' recall. The interpretation of the ICC levels could be questioned as different limits have been suggested [24]. Given the uncertainty surrounding the clinically acceptable level of reliability, establishing limits remains arbitrary. Notably, the lowest ICC results in our study were observed for the VOIs ventrally and posteriorly of the cup in contrast to the VOIs medially and laterally corresponding to Digas zones. One possible explanation could be that the cup positioning does not preserve much bone, at least ventrally, making it more challenging to measure these areas with high precision.

The Bland-Altman plot intervals are relatively large, suggesting moderate precision in our study. The accuracy varies considerably between VOIs and observers. One possible explanation for this variation could be the comparatively low resolution of the images, along with the presence of outliers for

both observers. This study is still the first to report on the precision of periprosthetic acetabular F-PET. The CVs% observed in previous studies on lumbar F-PET ranged from 9.2% to 10.1% [1, 130].

ICC and CV are statistical measures used to assess reliability and variability in data. ICC, commonly used in inter-rater reliability, evaluates the consistency or reliability between measurements and ranges between 0 and 1, where 0 is no reliability and 1 is perfect reliability. On the other hand, CV is useful for understanding the extent of variability in a data set. A low CV indicates less variability relative to the mean, whereas a high CV denotes greater variability.

General discussion

Clinical outcome after THA is excellent. However, arthroplasty registries show that the outcome in younger patients is not as good as in older patients [166]. In developed countries, the average life expectancy and expectations for an active lifestyle also increase in older age groups. Consequently, an increase in the demand for hip arthroplasties is anticipated. Implant design and pharmacological intervention could play a crucial role in conserving the local biological environment to reduce possible implant failure and facilitate subsequent reoperations. The implants studied in this thesis were designed to preserve proximal bone (CFP stem) or with a finish and surface thought to enhance bone ingrowth in the acetabulum (Continuum cup and TOP cup). However, we observed periprosthetic bone loss around all these implants.

In the DATA study, we investigated the effect on pBMD for 2 doses of denosumab postoperatively (6 months apart), with a positive effect only during the treatment period of up to 1 year, observing afterwards a rebound effect on pBMD after discontinuation of denosumab. Interestingly, we observed a similar effect in both the proximal femur (study I) and the acetabulum (study II). It is yet unknown how long the treatment with denosumab should continue to maintain the positive effect on pBMD or if switching to another antiresorptive medication could be a better alternative. Our institution investigated whether denosumab modulates the inflammatory response after THA, but only found a significantly increased expression of RANKL in the treatment group [135]. This could explain the rebound effect observed in the rapid loss of pBMD upon discontinuing denosumab treatment. Apart from RANKL and tumor necrosis factor receptor super family member 9 (TNFRSF9), no other inflammatory protein (of 92 detected inflammation-related proteins) was significantly affected by denosumab treatment [135].

The clinical relevance of stress shielding is unknown. No studies have shown a link between a decrease in pBMD and revision rate or clinical outcome. More studies on the long-term effects of pBMD loss are needed to establish whether this is a real clinical problem.

However, the proximal pBMD loss observed in studies I-III occurred in the most common location for osteolytic lesions and osteolysis, is a primary factor contributing to the need for revision surgery after THA [112]. Previous studies have demonstrated a link between PE wear and osteolysis, where periprosthetic osteolysis was a risk factor for implant loosening and poor clinical outcome after THA [40, 57].

F-PET is an effective, non-invasive method that quantifies bone formation in any skeleton site, including the periprosthetic bone. Notably, femoral pSUV increased in both groups compared to baseline (study I), but acetabular pSUV was reduced for both the placebo- and denosumab-treated patients (study II). An explanation for these differences in postoperative findings of pSUV of the acetabulum and proximal femur could be that the proximal part of the hip joint, the acetabulum, is close to bone affected by OAH. In contrast, the femoral head affected by OAH, the distal part of the OAH-affected hip joint, is resected and replaced [150, 151], implying that the investigated part of the proximal femur is not exposed to the same extent as the acetabulum to the changes due to OAH.

Study IV proposes a standardized methodology for analyzing quantitative, periprosthetic F-PET around acetabular THA components. A standardized method is critical for comparing studies and establishing SUV thresholds for septic and aseptic loosening diagnostics. With limited training, 2 orthopedic surgeons could analyze the results for periprosthetic SUV with good inter- and intraobserver reliability and high agreement, establishing F-PET as a reliable and useful tool in the clinical investigation of hip arthroplasty.

Conclusions

Administering 2 subcutaneous denosumab injections, spaced 6 months apart following uncemented THA, effectively prevents pBMD decline at the acetabulum and proximal femur for the first year. However, the effects are not enduring. Based on our findings, 2 doses of denosumab to inhibit pBMD loss after uncemented THA cannot be recommended.

Our results demonstrate an inferior long-term survival rate for the TOP cup compared to retrospective studies with the same implant and an inferior survival rate compared to the survival rates from other uncemented acetabular implants. Moreover, the TOP cup cannot prevent periprosthetic bone loss.

F-PET of acetabular cups can be reliably performed with strong agreement and moderate precision using the QHPR software. Periprosthetic F-PET shows promise in assisting the clinician with suspected implant loosening or infection.

Future perspectives

Long-term follow-up of the DATA study using DXA, radiography and clinical measures is planned. The 2-year follow-up showed proximal bone loss around the CFP stem and the Continuum cup when denosumab treatment was discontinued. Long-term follow-up will reveal whether this bone loss will continue. However, we still do not know whether bone loss of pBMD constitutes a clinical problem. The clinical consequences of this pBMD loss remain to be proven and investigated further.

Future research in THA is proposed to focus on whether patients could benefit from treatment with denosumab or other antiresorptive drugs after THA and, if so, for how long.

Moreover, the association between polyethylene wear, periprosthetic bone loss and revision in uncemented cups should be investigated.

Future studies should continue searching for clinical applications of F-PET and standardized ways to analyze images. It would be valuable to determine the precision of periprosthetic F-PET with double measurements and patient repositioning.

Summary in swedish – Sammanfattning på svenska

Belastningsrelaterad smärta och värk i höftleden, nedsatt rörlighet, gångsträcka och livskvalitet är symtom på höftledsartros. Konservativ behandling ger lindring. När denna behandling sviktar, är operation med total höftledsprotes en mycket framgångsrik metod med positiv effekt, där 95% av implantaten fortfarande fungerar efter 10 år.

Frekvensen av höftprotesoperationer har successivt kraftigt stigit och i Sverige utfördes år 2022 drygt 20.000 ingrepp. Förankring av proteskomponenter kan ske antingen med hjälp av bencement, s.k. cementerad fixation, eller på biologisk väg där implantatet kilas fast i benet, s.k. ocementerad fixation. Ocementerade höftproteser förlitar sig till absolut primärstabilitet genom ”press-fit” initialt och sekundärt genom beninväxt i den mikroporösa titanytan. Biologisk förankring kräver bra benkvalitet och används oftast för yngre patienter.

Världen över, tenderar antalet operationer med ocementerade protesimplantat att öka. Ocementerade implantat är dock associerade med minskning av protesnära bentäthet. Därmed finns potentiell risk för protesnära frakturer.

Denna avhandling fokuserar på ocementerade höftproteser. Huvudmålen har varit att undersöka om man kan förhindra minskning av protesnära bentäthet, efter ocementerad höftprotesoperation, med hjälp av läkemedel mot benskörhet (studier I och II) och i ett längre perspektiv undersöka resultaten av protesnära bentäthet och ”8 års-överlevnad” av en ocementerad ledskål (studie III). Dessutom har vi utvärderat precisionen och överenstämmelsen av analys med positronemissionstomografi (PET) för olika undersökare (studie IV).

Vi genomförde en dubbelblind, placebo kontrollerad prövning där 64 patienter, som opererades med en ocementerad CFP stam (studie I) och en ocementerad Continuum ledskål (studie II), lottades till två injektioner med placebo eller två injektioner med en monoklonal antikropp, denosumab, som har bromsande effekt på de bennedbrytande celler. Patienterna följdes upp i 2 år med mätning av bentäthet, analys av PET och blodprover för analys av markörer för benomsättning. Våra resultat visade att denosumab motverkar förlust av bentäthet både runt stammen (studie I) och runt ledskålen (studie II), men effekten är övergående efter avslutad behandling. Dessutom, uppvisade patienter som fått denosumab en tydlig minskning av både lokal (analyserat med

PET) och systemisk benomsättning (undersökt med blodprover). Båda patientgrupper var lika nöjda med resultatet av operationen.

Studie III är en prospektiv studie för att utvärdera de 8 års resultat av den ocementerade TOP ledskålen med avseende på implantat överlevnad, protesnära bentäthet och kliniska utfallsmått. Efter 8 år hade endast 25 av 30 (83%) patienter fortfarande fungerande implantat och vi observerade en fortsatt minskning av bentäthet på de proximala områden runt ledskålen. Patienterna som inte genomgått en revision (omoperation) var nöjda med operationsresultatet.

Studie IV är en metodologisk studie med mål att utvärdera precisionen och överensstämmelsen av PET bilder. Två oberoende undersökare har analyserat samtliga PET bilder från studie II, två gånger med minst 3 veckors avstånd mellan analyserna. PET-analys av ledskålen visade sig vara pålitlig, med hög överenstämmelse för, och mellan, undersökare.

Denna avhandling visar att två doser av denosumab kan effektivt minska förlust av bentäthet runt CFP stammen och Continuum ledskålen och även minska benomsättning. Effekterna efter behandlingens avslut är dock inte bestående. Om varaktig prevention av minskning av protesnära bentäthet eftersträvas, tillrådes nya studier med förlängd behandlingstid eller andra farmaka. Dessutom, fungerar TOP ledskålen under kortare tid jämfört med vad som rapporterats för flertalet andra ocementerade ledskålar och minskningen av protesnära bentäthet fortsätter mellan 2 till 8 år. Slutligen, konkluderar vi att PET av ledskålar är en pålitlig metod som kan användas när analys av benbildning kring implantat är av intresse.

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