Hip arthroplastic surgery provides excellent results in terms of relieving pain and restoring motion. However, it affects proximal femoral biomechanics and causes changes to proximal femoral bone mineral density. The main purpose of this dissertation was to study these bone mineral density changes in proximal femur after total hip arthroplasty, hip resurfacing arthroplasty and if bisphosphonates could have an affect to the proximal femoral bone loss.
BONE MINERAL DENSITY CHANGES AND HISTOMORPHOMETRIC FINDINGS AFTER HIP ARTHROPLASTIC SURGERY
BONE MINERAL DENSITY CHANGES AND HISTOMORPHOMETRIC FINDINGS AFTER HIP ARTHROPLASTIC SURGERY

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ABSTRACT

Periprosthetic bone loss and bone mineral density (BMD) changes are well-known phenomena after hip replacement surgery. These changes in BMD are thought to be mainly because of stress shielding. The scale of these changes depends widely on patient and implant-related factors. The bone mineral density changes are most significant during the first year after surgery. The results after hip arthroplasty are good to excellent in long term follow-up. In the year 2018 1537 hip revisions were made in Finland according to the Finnish Arthroplasty Register. Up to 9.1% of patients underwent a revision within 10 years of the index hip arthroplasty in the 21st century. The main reasons for revision surgery are infection, dislocation, periprosthetic fractures and aseptic loosening of the implant. The relationship between bone mineral density changes and clinical outcome is unclear.

The main aims of this doctoral thesis were to determine the BMD changes in long term follow-up after total hip arthroplasty (study I), what happens to the BMD in the femoral neck area after hip resurfacing arthroplasty (study II), can postoperative BMD loss be affected by administrating bisphosphonates after hip arthroplasty (study III) and is there a correlation between bone turnover parameters and postoperative BMD loss after THA (study IV).

We found that after the first postoperative year there were changes in BMD but these changes reflected the normal aging process of the bone. In terms of periprosthetic bone loss hip resurfacing arthroplasty seems to be a more physiological option i.e. the BMD changes in the femoral neck area were minimal one year after surgery. Bisphosphonates seem to minimize the BMD decrease after THA and the effect lasted up to five years postoperatively. Regarding bone turnover in patients with OA it seems that the higher the bone volume was in both the iliac crest and in the proximal femur at the time of arthroplasty, the less the BMD loss was postoperatively. Other bone histomorphometric parameters did not correlate with the BMD postoperatively.
TIIVISTELMÄ


Tämän tutkimuksen tarkoituksena oli selvittää luun mineraalitiheyden muutoksia pitkällä aikavälillä lonkan tekonivelleikkauksen jälkeen (I), mitä reisiluun kaulan luontiheydelle tapahtuu lonkan pinnoitetekonivelleikkauksen jälkeen (II), voiko leikkauksenjälkeisen luukatoon vaikuttaa osteoporoosilääkityksellä (III) ja vaikuttaako luun aiheenvaihdunta proteesin vieressä luukatoon (IV).

Tulostemme mukaan ensimmäisen postoperatiivisen vuoden jälkeen luuntiheysmuutokset ovat lievempiä ja heijastavat normaalia ikääntymisprosessia. Lonkan pinnoitetekonivelleikkaus vaikuttaa ovelan luun mineraalitiheyteen vähemmän vaikuttavalla leikkausmenetelmällä. Osteoporoosilääke (alendronaatii) lonkan tekonivelleikkauksen jälkeen annettuna näyttää vähentävän tyypillistä leikkauksenjälkeistä luukatoa ja lääkityksen vaikutus saattaa ulottua viiteen vuoteen saakka leikkauksen jälkeen. Luukudosnäytteestä tutkittuna luun aineenvaihdunta leikkaushetkellä näyttää ennustavan huonosti leikkauksenjälkeistä luukatoa.
Luokitus: WE 202, WE 860, WE 862, 865
Yleinen suomalainen asiasanasto: leikkaushoito, lonkka, luuntiheys, tekonivelet
To Elina and Ahti
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Kuopio 6th of September 2019
Toni Tapaninen
LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications which are referred to in the text by their Roman numerals:


IV  Tapaninen T, Hatakka V, Xiaoyu T, Burton I, Kröger H. Bone histomorphometric findings in the iliac crest bone and in the proximal femur in patients with osteoarthritis. Submitted

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ABBREVIATIONS

BMD     Bone mineral density
BMC     Bone mineral content
DXA     Dual x-ray absorptiometry
FNN     Femoral neck narrowing
HRA     Hip resurfacing arthroplasty
HRT     Hormone replacement therapy
NHS     National Health Service (UK)
NSAID   Non-steroidal anti-inflammatory drug
MoM     Metal-on-metal
OA      Osteoarthritis
OARSI   Osteoarthritis research society international
PTH     Parathyroid hormone
QALY    Quality adjusted life year
ROM     Range of motion
ROI     Region of interest
THA     Total hip arthroplasty
UK      United Kingdom
WOMAC   Western Ontario and McMaster Universities Arthritis
1 INTRODUCTION

The amount of people suffering from osteoarthritis (OA) is constantly growing. The main joints affected by this disease are the hip, the knee and the hand. It is estimated that in the UK almost 2.5 million people are affected by hip OA and in the U.S. more than 10% of the population has clinical OA. In Finland 5.7% men and 4.6% of women aged over 30 years suffer from OA and from over 75-year old people almost 20%. In the year 2018 9631 primary hip arthroplasties were performed in Finland, and the numbers are growing as the population ages (Finnish Arthroplasty Register, www.thl.fi/far). OA has also a significant economic impact. In the U.S alone joint replacement surgeries had a cost of $42.3 billion. According to Finnish Institute of Health and Welfare the estimated cost from hip replacement is somewhere between 60-70 million euros annually. (Arokoski et al. 2007, Murphy et al. 2012, Murray et al. 2013)

Hip arthroplasty was named “the Operation of the Century” in Lancet 2007. Naming hip arthroplasty in such a flamboyant way reflects well its potential to increase the ability to return to physical activities and to ease the pain and stiffness associated with hip OA. The long-term results of hip arthroplasty are considered good to excellent and the complication rate is relatively low. It appears to be also very cost effective when measured by its ability to provide quality-adjusted life years. (Cavagnaro et al. 2017, Lavernia et al. 2015, Learmonth et al. 2007)

However, hip replacement surgery can lead to serious and devastating complications and further to revision surgeries. The complication rate after revision surgery is higher and overall survival lower than after primary surgery. The four main reasons that lead to a revision surgery after a hip arthroplasty are infection, dislocation, aseptic loosening of the implant and periprosthetic fractures. According to the Finnish Arthroplasty Register in the year 2018 21.7% of revisions were made due to infection, 19.1% due to dislocation, 15.8% due to aseptic loosening of the implant (both the femoral and acetabular component) and 12.9% due to periprosthetic fractures (Finnish Arthroplasty Register, www.thl.fi/far). It is estimated that approximately 3.5% of patients have a periprosthetic fracture within 10 years from surgery and 3-10% of patients suffer from aseptic loosening of the implant within 15 years from surgery. It seems that the main reasons to these adverse events are because of the initial surgical trauma, implant-related wear debris and a phenomenon called stress-shielding. (Marshall et al. 2014, Pulido et al. 2008)

The stress shielding phenomenon is caused by the alteration in mechanical stimulus in the bone adjacent to the implant following placement of the implant. Typically the body weight shifts non-anatomically and non-physiologically towards the distal end of the implant resulting in changes in periprosthetic bone mineral density (BMD). Most of these changes tend to happen in the first postoperative year and can mainly be seen as a reduction in BMD in the proximal femoral area. The more anatomic the implant is the less periprosthetic bone loss occurs. Stress shielding
is widely documented in the first postoperative year and in middle-term follow-ups but there are quite little data suggesting what will happen in the long run. (Sumner et al. 2015)

Dual x-ray absorptiometry (DXA) was first designed to be a method to study bone mass and BMD in osteoporosis. Since then the technology has evolved so that DXA can also be used to investigate periprosthetic changes after joint replacement surgery. It has been proven to be safe and precise method. (Kröger et al. 1996)

Hip resurfacing arthroplasty (HRA) once gained huge popularity among orthopaedic surgeons in the first decade of 21st century. It was designed to be an alternative to conventional THA when treating young and more active patients. It was considered more anatomic and more physiological and partly because it caused less bone mineral changes around the implant. The preliminary results were promising in the terms of patient reported outcomes and implant survival. Unfortunately, the problems related to the metal-on-metal bearings stopped the use of this type of implants entirely. The poor survival of these implant was almost entirely due to adverse tissue reaction to metal particles. The reaction can manifest in pseudotumors, capsular thickening and general metallosis. These tissue reactions are called ARMeD (Adverse Reactions to the Metal Debris). The use of HRAs in Finland have ceased entirely because of these problems. (Dunbar et al. 2014, Langton et al. 2011, Shimmin et al. 2008, Vendittoli et al. 2006)

Bisphosphonates are potent drugs to enhance bone quality in osteoporotic patients. They have been shown to increase BMD and thus prevent osteoporotic fractures. Since there are several problems associated with poor bone quality after hip arthroplasty, bisphosphonates have been regarded as one option to preserve the periprosthetic BMD after hip replacement surgery. Previously there were a few studies indicating that in fact alendronate could prevent the early periprosthetic bone loss, but the follow-up time was restricted to the first postoperative year. (Lin et al. 2012, Shetty et al. 2006, Trevisan et al. 2010)

OA is often considered a “bone forming” disease meaning that both the bone volume and bone stiffness are increased in case of this condition. It was often thought that patients could not have both OA and osteoporosis, but nowadays it is known that both OA and osteoporosis can occur at the same time. It seems that the increase in the bone volume in OA is caused mainly by the formation of osteophytes (i.e. “new bone”) instead of decrease in bone resorption. (Gevers et al. 1989, Jordan et al. 2003) It is not known, whether general bone turnover in OA patients affects BMD changes around femoral implants.

This thesis aimed to determine the long-term BMD changes after total hip arthroplasty (THA) (study I). We were also interested in whether HRA preserved BMD better than conventional hip replacement in terms of BMD (study II). We also studied if alendronate given in the postoperative period showed a long-term bone preserving effect (study III) and whether periprosthetic bone loss could be predicted based on perioperative bone turnover rate measured by bone histomorphometric parameters within the iliac crest bone and in the proximal femur (study IV).
2 REVIEW OF THE LITERATURE

2.1 PROXIMAL FEMORAL BIOMECHANICS

It has long been observed that the structural composition of the femur adapts in response to the mechanical environment that it is subjected to. Cortical bone is formed from a layer of low porosity, high stiffness bone. Trabecular bone is formed from a series of struts, giving rise to a structure in which there is a spacial variation of continuum level porosity and directionally dependent stiffness throughout the femur. Both the varying thickness of the cortical bone and the structural properties of the trabecular bone are thought to be a result of the forces placed on the femur, which include the joint contact forces at the hip and knee joints, and muscle forces, which act on the cortex of the femur. (Phillips et al. 2011)

The structure of trabecular bone in particular follows trajectories of compressive and tensile stress, resulting in an optimised structure (Figure 1). In his work the Law of Bone Remodelling Wolff produced a trajectory diagram of the proximal femur in which trajectories met at right angles, the implication at a continuum level being that trajectories occur along lines of principal stress. (Wolff et al. 1892)

This trabecular structure changes throughout the lifetime. Any alterations to a mechanical stimulus, for example because of a hip prosthesis, cause significant changes. Also aging causes a decrease in BMD and loss of trabecular structures. It is crucial to understand proximal femoral biomechanics in order to study changes in it.

Figure 1. Projection of the proximal femur, showing the cortical (red) and trabecular bone (gray) on the left and representations of the trabecular arrangement in the proximal femur based on Wolffs original paper on the right (Nawathe et al. 2015, Wolff et al. 1892).
2.2 HIP OSTEOARTHRITIS

OA is a degenerative joint disease that causes progressive damage to articular cartilage and surrounding structures. The hip is the second most commonly affected joint (after the knee). It causes significant disability and limitations in activity. The etiology of OA is still unclear. OA is one of the most frequent conditions causing disability among adults. More than 10% of the adult U.S. population had clinical OA in 2005 and in 2009 OA was the fourth most common cause of hospital admissions. In the UK hip OA affects almost 2.5 million people according to NHS (National Health Service, UK). OA has also a significant economic impact. In the U.S it is estimated that hip and knee replacement surgeries had a cost of $42.3 billion in the year 2009. These numbers are growing (Murphy et al. 2012, Murray et al. 2013).

In Finland it is estimated that 5.7% of men and 4.6% of women over 30-years old suffer from hip OA. People over 75-years almost 20% suffer from OA (Arokoski et al. 2007). A total of 9631 primary hip arthroplasties were performed in Finland in the year 2018 (Finnish Arthroplasty Register, www.thl.fi/far).

Hip OA is usually defined from radiographic information and clinical symptoms. Radiographic OA is based on information from plain x-rays and can be defined with either individual features or, more commonly, the Kellgren–Lawrence scale, where radiographic OA is classified as mild (grade 2: joint space narrowing and osteophytes seen on X-ray), moderate (grade 3: many osteophytes, joint space narrowing, sclerosis, and possible bone contour deformity), or severe (grade 4: large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone contour deformity). Typically, OA is defined as a Kellgren–Lawrence grade of 2 or higher. Symptomatic OA is defined as the combination of radiographic evidence of OA and symptoms (pain, stiffness) in the radiographically affected joint. Overall, the concordance between pain and radiographic evidence is only modest to moderate meaning that many people have radiographic evidence of OA but no symptoms and vice versa (Felson et al. 2004, Hannan et al. 2000).

Hip OA is associated with other diseases, but there is often no proven causal relationship. A population-based cohort study showed that hip OA is associated with frailty, with an odds ratio after adjustment for confounding variables of 1.6 (95% confidence interval 1.1 to 2.2). Hip OA is also associated with an increased risk of all-cause mortality (hazard ratio 1.14) and higher rates of mental health problems. One large, population-based cohort study also suggests an increase in cardiovascular mortality associated with OA (hazard ratio 1.24). A prospective, population-based cohort study suggests this is probably because of ensuing disability rather than the presence of OA itself. (Barbour et al. 2015, Cook et al. 2007, Hoeven et al. 2015, Wise et al. 2014)

Hip OA can be managed in many different ways, depending on the patient. Patients often see OA as a function of age rather than a medical disorder, and younger patients are often more distressed and frustrated with managing the disease.
Osteoarthritis Research Society International (OARSI) recommends a combination of both pharmacological and non-pharmacological methods to treat hip OA. In the recent OARSI guidelines the recommended core treatments to hip OA are arthritis education and structured land-based exercise programs. The mainstay of surgical treatment is THA. (Ballantyne et al. 2007, Bannuru et al. 2019, Bozic et al. 2013, NHS Decision aid 2010, NICE Guideline CG59 2008, Gignac et al. 2006, Zhang et al. 2008)

Conservative treatment can be non-pharmacological or pharmacological. Non-pharmacological methods are weight loss and physical therapy. Several studies demonstrate improved function and a reduction in disability after weight loss in patients with knee OA. A meta-analysis of 35 trials suggests weight loss of >5% is associated with a significant reduction in patient self reported disability due to knee pain. There is less robust evidence of improved function with weight loss for hip OA. Nevertheless, expert consensus recommends weight loss in patients with hip OA, through a reduction in caloric intake, enrolment in weight loss organizations, and non-joint loading exercises such as swimming. (Christensen et al. 2005, Christensen et al. 2007, Messier et al. 2004, Zhang et al. 2008)

Increasing muscle strength improves the mechanical environment and reduces joint loading of an arthritic hip. A Cochrane review found that completion of a supervised physiotherapy program reduces pain and improves physical function in patients with mild to moderate pain from hip OA. The benefits of supervised physiotherapy programs are small but are shown to last three to six months after treatment. (Fransen et al. 2014).

A variety of analgesics, including paracetamol, NSAIDs, and opioids are used to manage pain. A Cochrane review looked at 15 trials that evaluated the use of paracetamol versus placebo and NSAID in treating hip OA. Compared with placebo, paracetamol led to only a small reduction in pain (standardized mean differences 0.13 (95% CI 0.22 to 0.04)). NSAIDs were moderately superior to paracetamol in pain reduction, physican global assessments, and functional status. The superiority of NSAIDs was more marked in severe OA. NSAID groups had a higher rate of gastrointestinal events (relative risk 1.47), but otherwise there was no significant difference in safety between paracetamol, placebo, and NSAIDs. In the recent OARSI guidelines NSAIDs are recommended, paracetamol is conditionally not recommended and opioids are strongly not recommended. (Bannuru et al. 2019, Towheed et al. 2006).

### 2.2.1 Development and risk factors of osteoarthritis

Also called degenerative joint disease and osteoarthrosis (because of the inconsistency of inflammation), OA is a disease of the whole joint in which all articular structures are affected. Early in the disease, the pathologic events are dynamic. Injured cartilage mounts an attempt at increased matrix synthesis and repair while exuberant osteophytes stabilize the joint, preventing injurious instability. Clinically, a person with an episode of osteoarthritic joint pain may begin
a program of rehabilitation or may simply stop the activity that caused joint pain, possibly resolving the episode of pain. Late in disease, most of the joint structures have experienced irreversible pathologic changes, and OA is best conceptualized as total joint failure. The transition from a dynamic to an irreversible process varies greatly from joint to joint and person to person and, in many persons, may never occur. These notions of disease describing it as dynamic and affecting all joint structures replace the concept of OA as being inevitably progressive and affecting hyaline articular cartilage predominantly. Hyaline articular cartilage loss is a signature event in OA. (Felson et al. 2004).

Several OA risk factors can be divided into general, intrinsic, and extrinsic. Age, sex and genetics are considered as general factors. It seems that OA is more common in Caucasian population than it is among Asian population. (Allen et al. 2010). Hip OA is more common in women than in men, and genetic studies show a 50% heritability in European population. Incongruency of the joint (such as dysplasias) and joint laxity are intrinsic factors. They accelerate articular degeneration because of abnormal wear and loading. Extrinsic factors such as increasing body mass index, high levels of certain exercise, and heavy manual labour are thought to increase the incidence and progression of hip OA.

Most often the cause of hip OA is multifactorial. A series of risk factors lead to instability, malalignment, increased joint load, microtrauma and structural damage. The joint responds through subchondral and synovial inflammation, and bone hypertrophy. This is visible on radiographs as narrowed joint space, sclerosis, and cyst or osteophyte formation. (Arokoski et al. 2007, Croft et al. 1990, Felson et al. 2004, Hippsley-Cox et al. 2009, Juhakoski et al. 2009, Oliveria et al. 1999, Vingård et al. 1993)

2.3 HIP ARTHROPLASTY

Hip arthroplasty is one of the most commonly performed and successful operations in the world. It involves removing the articular surfaces of the joint and replacing them with prostheses.

The first attempt to treat hip OA surgically was made more than 100 years ago. Interpositional arthroplasty, offered in the late 19th and early 20th centuries, entailed replacing various tissues—including fascia lata, skin, and even the submucosa of pig’s bladder—between the articulating surfaces of the hip. (Smith-Peterson et al. 1948) Interposition of a vitallium cup, which covered the reshaped femoral head, by Smith-Peterson in 1938 heralded a new era of arthroplasty. Charnley revolutionised management of the arthritic hip with the introduction of low friction arthroplasty. He made three major contributions to the evolution of total hip replacement: 1) the idea of low friction torque arthroplasty; 2) use of acrylic cement to fix components to living bone; and 3) introduction of high-density polyethylene (PE) as a bearing material. In a review of the first-generation results of Charnley’s low friction arthroplasty survivorship was 77-81% after a 25-year follow-
up, with revision of any component as the endpoint. (Learmonth et al. 2007) Similar data have been reported by other researchers. These findings lend support to Coventry's observation in 1991 that “Total hip arthroplasty, indeed, might be the orthopaedic operation of the century”. (Coventry et al. 1991)

In the majority of OECD countries the utilization of hip arthroplasty exceeds 200/100,000 population. Hip arthroplasty has continued to increase in all age groups. The growth rate in patients aged 64 years and younger was seven-fold higher than in older patients. (Pabinger et al. 2014)

2.3.1 Total hip arthroplasty (THA)

The purposes of THA are hip pain relief, resumption of range of motion (ROM) with normal ambulation, and long-term implant survival.

THA is indicated for patients who failed to respond to non-surgical management options such as pharmaceutical treatments (e.g., analgesics, anti-inflammatory agents, steroid injections, topical treatments), self-management, patient education, acupuncture, exercise, physical therapy, or manual therapy. This procedure involves the replacement of a damaged hip joint with an artificial hip prosthesis consisting of an acetabular cup (with or without a shell) femoral stem, and femoral head.

In the 1960s, total hip replacement revolutionised management of elderly patients crippled with arthritis, with very good long-term results. Today patients are hoping to restore their quality of life and continue normal physical activities by undergoing hip replacement surgery. Advances in bioengineering technology have driven development of hip prostheses. Both cemented and uncemented hips can provide durable fixation and good long-term results. Universal economic constraints in healthcare services dictate that further developments in THA will be governed by their cost-effectiveness. (Learmonth et al. 2007)

THA is proven to be cost effective treatment for hip OA and the survival rates of new modern prosthesis are excellent. The patient reported outcomes are also in a high level. Many of the modern conventional prosthesis provide over a 90% survival rate of the prosthesis during a long-term follow-up, but some MoM devices provide only an 81.4% survival (BHR) or even 45.1% survival (ASR) rate after ten years of follow-up. (Cavagnaro et al. 2017, Finnish Arthroplasty Register 2018).

There is very good evidence showing that THA is really cost effective. In the U.S. patients with better Western Ontario and McMaster Universities Arthritis (WOMAC) scores had an estimated quality-adjusted-life year (QALY) cost of approximately $8000/QALY-gained and even in those with worse WOMAC scores the cost was approximately $26000/QALY-gained. Thus even when performed in the older and “sicker” patients THA was shown to be very cost effective (Lavernia et al. 2015).

The THA can be divided roughly in two different groups roughly according to the fixation method. Either it can be cemented or uncemented THA. The optimal method of fixation for primary THA, particularly fixation with or without the use of
cement is still controversial. Also there are different kinds of materials used especially in the femoral implant. Most of the implants are made of cobalt chrome, steel or titanium alloys. Titanium provides a slightly more elastic fixation that better reflects normal bone elasticity. The intention to find more bone preserving implants has lead to the development of the hydroxyapatite-coated femoral implant. It was designed to provide faster osteointegration and more metaphyseal load thus preserving proximal femoral bone stock (Van Der Wal et al. 2008).

In a systematic review and meta-analysis of all randomized controlled trials comparing cemented and uncemented THA available in the published literature, there is no significant overall difference between cemented and uncemented THAs in terms of implant survival as measured by the revision rate. It seems, however, that in the elderly cemented THA has a better implant survival and lower complication rate (Abdulkarim et al. 2013, Mäkelä et al. 2014). Nevertheless in the 2006 Cochrane review they stated that cemented prosthesis may reduce postoperative pain and lead to better mobility. These findings can only be seen in the short-term follow-up (Parket et al. 2006).

2.3.2 Hip resurfacing arthroplasty (HRA)

The hip resurfacing concept was developed originally by British orthopedic surgeon Derek McMinn in 1989, with the first patient implantation in 1991. Since THA shows excellent results in elderly patients but in younger patients they are poorer, the HRA was originally developed for young and active patients, especially for femoral bone stock preservation. The acetabular cup acts in the same way as in THA, but the femoral head is resurfaced sparing the femoral neck. Complications in early versions finally led to the metal-on-metal bearing couple becoming the standard in HRA. At the turn of the century, HRA spread to Finland. The major advantages of HRA were thought to include femoral bone stock preservation, which was believed to make revision surgery easier; a low dislocation risk due to the large femoral head diameter; physiological hip loading, thus preventing stress shielding and early resumption of physical activities. Hip resurfacing facilitates almost complete proximal femur preservation — far more than short stems. On the acetabular side, the same amount of bone removal is required as with THA. However, it is difficult to demonstrate and prove the potential advantages in hip function since measuring devices and scoring systems are quite inaccurate. (Costa et al. 2012, Shimmin et al. 2008, Vendittoli et al. 2006)

A register study by Smith et al. published in Lancet 2012 showed that there are big issues with HRA. The long-term implant survival was only 72% at the 10-year follow-up. This high failure rate may be due to elevated functional demands of younger patients, which may lead to high wear and mobilization of the implant. (Smith et al. 2012).

Moreover, MoM HRA has a specific set of possible complications. Aseptic femoral failures were initially the most prevalent cause for revision but progress in patient selection and surgical technique seem to have resolved this problem. Wear-related
failures (high metal ion levels and adverse local tissue reactions, metallosis) are now the main concern. Wear-related failures are essentially associated with poor acetabular component design and orientation, to which MoM is more sensitive than other bearing materials. (Amstutz et al. 2015)

Due to recent problems associated with the MoM bearing, the use of HRA has vastly decreased. The high failure rates of large-diameter (i.e. 36mm and above) are well above those recommended for continued implant usage. This has also decreased the use of MoM bearing in conventional THA and in Finland the use of these types of implants is ceased completely. In a paper written by Dunbar it is suggested that the routine use of metal-on-metal hip resurfacing arthroplasty is no longer justified. The article shows clearly that all the assumed advantages in HRA are actually not proven. HRA does not lead to increased implant survival, it is not less invasive, it does not lead to easier revisions and does not have superior functional outcomes. The MoM HRA also has known problems with metal ion levels and adverse soft tissue reactions such as pseudotumors. (Dunbar et al. 2014)

2.3.3 Complications of hip arthroplasty

Complications after hip arthroplasty can be devastating to the patient, and they cause a huge economic burden. The overall complication rate after THA varies from 2% to 14%, depending on the study. Complications after hip arthroplasty can be either implant related or systemic. Usually the implant-related complications can be referred to as “implant survival”, which the “survived” implant has not been revised. This survival is often presented as a Kaplan-Meier estimate which measures the fraction of patients having an intact or unrevised implant. Up to 0.8% of patients at 5 years and 3.5% at 10 years experience a periprosthetic fracture after THA. This is principally due to severe periprosthetic bone loss, which is rare but results in severe consequences, such as reduced function, and increased morbidity and mortality. Furthermore, implant failure with aseptic loosening, in which wear debris-induced osteolysis plays a major role, can be expected in 3–10% of cases within 15 years.

Implant-related complications can be roughly divided into early and late complications. Early complications are mostly caused by poor bone quality and surgical quality (i.e. positioning the implant, medullar canal broaching, introducing the femoral component to the patient and implant stability) and late complications are mostly because of implant loosening, osteolysis and periprosthetic fractures. These complications are described in more detail in table 1.
The five most common implant related early and late complications after total hip arthroplasty

<table>
<thead>
<tr>
<th>Early (&lt; 1 year from index surgery)</th>
<th>Late (10 years from index surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dislocation/subluxation</td>
<td>Aseptic loosening</td>
</tr>
<tr>
<td>Periprosthetic fracture</td>
<td>Adverse reaction to particulate debris</td>
</tr>
<tr>
<td>Infection</td>
<td>Periprosthetic fracture</td>
</tr>
<tr>
<td>Aseptic loosening</td>
<td>Implant wear</td>
</tr>
<tr>
<td>Malalignment</td>
<td>Osteolysis</td>
</tr>
</tbody>
</table>

Table 1. The five most common early and late implant related complications after total hip arthroplasty (Online Annual Report NJR. 2018).

In a meta-analysis written by Pulido and coworkers the overall in-hospital complication rate was 10.6%. They divided the complications into systemic complications (such as cardiovascular or neurologic) and local complications (orthopedic complications). The rate of systemic complications was 7.1% and approximately half of these were considered major complications. The major systemic complications included possible life-threatening complications such as pulmonary embolism, cardiac arrest, myocardial infarction, stroke and anoxic brain injury. The rate of local complications was 3.5%. The majority of these local complications were deep periprosthetic infections, periprosthetic fractures and dislocations. (Pulido et al. 2008)

Death is a rare complication of hip arthroplasty. The in-hospital mortality rate following this surgery ranges from 0.16% to 0.52% in the United States. The 90-day postoperative mortality rate is ~1% after primary hip arthroplasty and ~2.5% after revision surgery. The mortality rate is higher in patients with cardiovascular diseases aged over 70 years. (Parker et al. 2008)

Nerve injury is also a rare complication, and there is no good data about its prevalence. There are some case series from the 1990s stating that sciatic nerve palsy, from mild weakness to a complete palsy, could be identified in almost 1.7% of arthroplasties over-all. (Parket et al. 2008)

Implant-related complications mostly lead to revision surgery. These conditions include aseptic loosening of the implant, periprosthetic fractures, periprosthetic infections and dislocations (Finnish Arthroplasty Register, www.thl.fi/far). In a recent systematic review by Marshall et al. the average time to revision was 3.0 years for metal-on-metal hip resurfacing and 7.8 years for conventional THA. National Joint Registry data from UK suggests the probability of needing a total hip replacement revision at 10 years is 4.99%. Around half of revisions occur as a result of aseptic loosening of the prosthesis, the main symptom of which is thigh or groin pain. Aseptic loosening can be readily diagnosed with radiographs. Aseptic loosening can be due to a variety of reasons, including patient-related factors (such as body mass index and activity level), surgical technique, and prosthesis design. (Marshall et al. 2014, NJR Online Annual Report 2018)
2.4 PERIPROSTHETIC BONE LOSS

The quality of hip replacement surgery is crucial. Both the femoral stem and acetabular cup have to be the correct size because it greatly affects to the implant stability. If primary implant stability is achieved, the overall survival of the prosthesis depends on its osseointegration. This osseointegration is influenced by the load, the characteristics of the implant and the bone-implant interface, and the quality and quantity of the periprosthetic bone. This may lead to a resorption process in bone areas that are no longer mechanically loaded. The bone loss is of concern as it may progress, and problems such as implant subsidence and periprosthetic fractures may follow. Poor quality of periprosthetic bone could also cause more complex revision surgeries if needed. Several factors affect the quality of periprosthetic bone, the most common of which are general osteoporosis, particle-related osteolysis and stress-shielding.

Gruen and colleagues evaluated periprosthetic bone loss from plain X-ray films investigating radiolucency around the prosthesis stem. Radiographs provide an image of the local bone changes, but the quantification of bone response is difficult and subject to many inaccuracies. The DXA-scan has been proven to be a better and more precise method for evaluating periprosthetic bone loss. (Kröger et al. 1996)

DXA -measurements have shown that there is a loss of 10% to 45% in periprosthetic bone mass after total hip arthroplasty. Aseptic loosening due to periprosthetic osteolysis is the most frequent known cause of late implant failure. Wear of prosthetic materials results in the formation of numerous particles of debris that cause a complex biological response. For example PE liners cause osteolysis and granulomatotic lesions around the prosthesis (Santavirta et al. 1998). Introduction of the prosthesis alters the physiological transmission of loads to the surrounding bone. Because of the altered loading pattern, the body weight shifts straight to the diaphyseal area, bypassing the femoral bone and resulting in a reduction of BMD through remodeling. Other risk factors for periprosthetic bone destruction include osteoporosis, rheumatoid arthritis and especially surgery. It has been shown that periprosthetic bone loss happens mostly in the first postoperative year. After that the BMD changes merely reflect a normal aging process. (Cavalli et al. 2014, Kroger et al. 1996, Kröger et al. 1998, Nysted et al. 2011)

There are also numerous metabolic factors that seem to associate with periprosthetic bone loss. The implant causes a chronic inflammatory reaction around the hip joint, and various transmitters (mostly interleukins) play a major role in the aseptic loosening of the implant. (Santavirta et al. 1998)

Many factors such as age, sex, underlying disease, quality of bone and type of implant may have an impact on remodeling, although the main determinant of bone mass distribution appears to be stress shielding.
2.4.1 Stress shielding

Originally the German anatomist and surgeon Julius Wolff developed Wolff’s law in the 19th century. It states that bone in a healthy person or animal will adapt to the loads under which it is placed. If loading on a particular bone increases, the bone will remodel itself over time to become stronger to resist that sort of loading. The internal architecture of the trabeculae undergoes adaptive changes, followed by secondary changes to the external cortical portion of the bone, perhaps becoming thicker as a result. The inverse is true as well: if the loading on a bone decreases, the bone will become less dense and weaker due to the lack of the stimulus required for continued remodeling. This reduction in bone density (osteopenia) is known as stress shielding and can occur as a result of a hip replacement (or other joint replacement). The normal stress on a bone is shielded from that bone transferred the prosthetic implant. (Frost et al. 1994, Wolff et al. 1892)

The survival and long-term success of the endoprosthesis depends upon many factors, including successful osseointegration of the prosthesis in the host skeleton. Stress shielding is a well-known mechanical phenomenon. It is caused by an alteration in the mechanical stimulus in the bone adjacent to the implant following placement of the implant (Figure 2.). The altered mechanical environment is thought to drive a subsequent adaptive response in the bone so that the bone structure and density more appropriately match the mechanical needs. In general, studies of stress-shielding have shown that the relative bending stiffness of the implant and bone is a key factor meaning that implant size and shape as well as material composition and bone size, shape and density are important. (Nysted et al. 2011, Sumner et al. 2015)

Implant design greatly affects the stress shielding phenomenon. Implant stiffness, materials used to manufacture the implant, stem length and possible porous coating all change the way the prosthesis is fixed to the bone and how much stress shielding it causes. However there is insufficient data comparing different types of implants. The design goal is to make the load transfer from the femoral stem to the host skeleton occur as proximally as possible, thereby minimizing reduction in mechanical stimulus to the host femur. (Sumner et al. 2015)
Figure 2. The stress shielding phenomenon, occurring as a result of the implant-induced change loading of the host bone following placement of a femoral stem in the proximal femur. The red, yellow and green areas indicate the load characteristics. Green denotes the unloaded parts and red denotes the more highly loaded regions of the proximal femur (Sumner et al. 2015).

Early designs of uncemented hip implants turned out to be failures mainly because the prerequisites for durable implant fixation were unknown. One exception was the chrome-cobalt stem of the Madreporic Lord prosthesis (Figure 3). Kaplan-Meier survivorship analysis with revision of the femoral component because of mechanical loosening, stem fracture, or radiographic loosening as the end point revealed a cumulative survival rate of 98% at 17.5 years. However, radiographic evaluation of the femoral bone that surrounds the stem revealed a high frequency of decreased density, mainly located in the proximal Gruen regions (1, 2 and 7) probably due to the excessive stress shielding related to the design of the implant. (Grant et al. 2004, Zügner et al. 2013)
2.4.2 Other types of periprosthetic bone loss

Not all bone loss in the periprosthetic region is associated with stress shielding. One of the factors affecting the periprosthetic bone is chronic inflammation process. Chronic inflammation process can cause bone loss and implant loosening similar to stress shielding. The pathogenesis behind this phenomenon includes wear of prosthetic compounds, such as PE, cobalt chrome, and titanium, which liberate particles from the implant surface. Most of these particles arise from the bearing couple, but if the prosthetic components are loose then it is possible that particles origin from the implant alone. These particles stimulate a chronic inflammatory response, which increases the bone-resorbing activity of osteoclasts and suppresses bone formation by osteoblasts, resulting in bone loss. Periprosthetic tissues contain granulomatous lesions dominated by inflammatory cells, particularly macrophages, and foreign-body giant cells. It is believed that an inflammatory reaction is initiated within the tissues in an attempt at particle clearance. This then becomes a chronic reaction, resulting in a granulomatous lesion. This granulomatous lesion in
Periprosthetic osteolysis often leads to the formation of a pseudosynovium-like structure, in which cells are organized into a lining layer in the membranous tissues adjacent to the failed implant surface. Juxtaposed to this pseudosynovium are fibrous and collagenous regions, possibly scar tissue, which could be indicative of late stage periprosthetic osteolysis. The plethora of factors released in this inflammatory reaction within the tissues contributes towards osteoclast formation. (Crotti et al. 2015, Santavirta et al. 1998)

Other types of periprosthetic bone loss include a series of phenomena caused by mechanical, thermal and chemical intraoperative damage that induce periprosthetic bone necrosis, which may take up to three months to repair.

2.5 BONE MINERAL DENSITY AFTER HIP ARTHROPLASTY

Periprosthetic bone mass and density can have an affect on implant survival and complication management. Evaluation of the periprosthetic bone density is possible by using DXA measurements. It is inevitable that there will be some periprosthetic bone loss after THA, but there are ways to minimize it.

2.5.1 Measuring bone mineral density after hip arthroplasty with dual-energy x-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) is a widely used method for the quantification of bone mass and BMD at the lumbar spine, proximal femur, and several other skeletal sites (Nuti et al. 1992). Two X-ray beams, with different energy levels, are aimed at the patient’s bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone. Developments in software analysis technique have enabled quantification of BMD adjacent to metal implants. However, the results from DXA scans vary greatly, depending on the positioning of the hip on the scan table. The first DXA studies after THA measured BMD preoperatively and immediately after the surgery. This may be an invalid method because preoperatively the possible stiffness of the hip joint can affect greatly to the positioning of the hip. Similarly, BMD measured too soon after the operation may cause similar problems. Also reaming the femoral canal causes periprosthetic bone loss. It is recommended to make the first DXA measurements postoperatively after the initial pain and stiffness of the joint due to the operation has mitigated and compare these results to the measurements at different follow-up points. (Kröger et al. 1998)

It was once thought that DXA can be used to measure periprosthetic BMD only on uncemented stems, because the cement may interfere and disturb the accurate measurement. However, several studies have shown that the DXA is adequately accurate both on cemented and uncemented stems. The precision error has been proven to be as little as 2.3% in case of uncemented prosthesis design and 2.5% with a cemented design. (Elvins et al. 1997, Kröger et al. 1996, Venesmaa et al. 2001)
DXA has been proven to be a precise method to quantify bone mass and density changes in the follow-up of THA. (Elvins et al. 1997, Kroger et al. 1996)

2.5.1.1 Bone mineral density after total hip arthroplasty

Both cemented and uncemented implants have resulted in a constant decrease of periprosthetic BMD in the proximal femur, especially over the course of the first postoperative year. Studies have shown that usually there is a loss of 10% to 45% of the periprosthetic bone mass during the first years after THA. This bone loss is not necessarily progressive. Some degree of restoration of bone density around implants usually occurs by two years, but there are also studies suggesting that after the first year the decrease in BMD is actually caused by the normal aging process of the bone. Bone loss is more persistent in the proximal part of the femur, which is thought to be caused by the stress shielding phenomenon. In a previous study by Venesmaa et al. it was shown that three months after the index surgery there was a 9.9% decrease in zone 1 and a 14.4% decrease in zone 7. Within one year postoperatively the decreases were 4.6-11.2% in zone 1 and 15.2-22.9% in zone 7. (Chandran et al. 2012, Dan et al. 2006, Venesmaa et al. 2001)

There are quite few studies investigating periprosthetic BMD changes in long-term. These few studies indicate, however that after the initial remodeling process, which seems to happen in the first postoperative year the BMD changes become less frequent and the BMD may reach a plateau stage. According to Merle et al., after five years postoperatively no significant changes in BMD can be seen in hips with a prosthesis or without. (Merle et al. 2011)

Periprosthetic BMD changes seem to be of similar magnitude in cemented and uncemented prostheses. (Chandran et al. 2012, Dan et al. 2006, Sabo et al. 1998, Venesmaa et al. 2001)

Not all stem designs act the same way in the proximal femur. Less proximal femoral bone loss occurred when using stems that were made of titanium rather than cobalt chrome in cemented THA, due to titaniums more elastic quality. Proximally coated uncemented stems with lower stiffness may cause less periprosthetic bone loss in the proximal femur. Proponents of short femoral-neck implants claim less interference with the biomechanics of the proximal femur, thus leading to smaller decrease in BMD after surgery. (Decking et al. 2008)

2.5.1.2 Bone mineral density after hip resurfacing arthroplasty

HRA was considered viable option to a standard THA, especially in younger and more active persons. HRA was thought to preserve BMD because of a more anatomical and physiological design. HRA enables a more natural loading of the femur without a stress-shielding pattern because of the preservation of the femoral neck.
There are several studies indicating that in fact the BMD both in the immediate femoral neck area and in the proximal femoral shaft is preserved after HRA surgery. It seems that within one year after surgery the BMD levels appear to be same as preoperatively and the BMD preservation continues up to five years from surgery. (Gerhardt et al. 2015, Håkkinen et al. 2011)

One potential risk after HRA is the femoral neck narrowing (FNN) or the “neck melting” phenomenon. According to Takamura et al. the prevalence of FNN after HRA is not clear and reports from the literature vary from 3.6% to 59%. The reason for FNN remains unclear and is thought to be multifactorial, representing adaptive remodeling due to stress-shielding, related to wear particles or caused by an insufficient blood supply as a result of a posterolateral surgical approach. Despite being considered a risk factor for a femoral neck fracture, there are some studies suggesting that it is actually a benign process and does not increase the risk of neck fractures or failure rates. (Lafosse et al. 2011, Spencer et al. 2008, Takamura et al. 2011)

2.5.1.3 General risk factors leading to revision surgery due to aseptic loosening

Poor implant osseointegration and aseptic loosening are two of the main reasons of hip arthroplasty revision surgeries. There are several systemic and local factors affecting the implant osseointegration.

It seems that the risk for revision surgery increases linearly as the patients age decreases. Although the increased risk of revision in younger patients has been almost entirely attributed to higher activity levels and higher loading on the joints, it is unknown whether other age-related factors that affect bone quality and contribute to the excess risk of revisions in young patients. (Labek et al. 2011)

The risk of revision due to aseptic loosening tends to be higher in women than in men in THA. We know from Finnish Arthroplasty Register that aseptic loosening is the most common cause for late revision on THA and that almost 60% of the revisions made in 2018 were in females. BMD is generally lower in women and this could be a reason for the higher risk of revision surgery. The relationship between osteoporosis or low BMD and aseptic loosening is still unclear. (Finnish Arthroplasty Register, www.thl.fi/far, Sadogi et al. 2013)

Obesity is the main risk factor for OA, and at least half of the arthroplasty patients are obese with a body mass index higher than 30 kg/m. Obesity is also associated with many adverse events in THA. The risk of aseptic loosening is about two times higher in obese patients, but the reason for this is yet unresolved. There are some opinions that this is due to increased mechanical stress of the implant and more frequent limb malalignment as well as lower activity levels in obese patients. (Electricwala et al. 2016)

Smoking and alcohol consumption can cause numerous adverse events after THA. Both smoking and excessive alcohol consumption have a detrimental effect on BMD, but there is no evidence that they increase periprosthetic BMD loss or that they are related to implant loosening (Kremers et al. 2016).
2.6 PREVENTION OF PERIPROSTHETIC BONE LOSS

One way to ensure a long service life of the prosthesis and prevent revisions is to focus on preventing the periprosthetic bone loss. Most studies have been performed using bisphosphonates. Bisphosphonates are widely used in the prevention and treatment of osteoporosis. Other indications include Paget’s disease, and metastatic bone disease. (Cummings et al. 1996, Hosking et al. 2004)

Mau-Moeller et al. studied the effect of physical exercise on postoperative BMD and found out that exercises that maintain the build up muscle mass could be useful in retaining postoperative BMD (Mau-Moller et al. 2015). Steens et al. showed that a shorter femoral neck prosthesis preserves the BMD in the femoral neck area better than conventional THAs. (Steens et al. 2015)

The use of bisphosphonate therapy in an effort to sustain and improve the clinical survival of total joint implants is of great interest. Wear-debris-induced osteolysis, stress shielding, immobilization, and operative trauma are the main mechanisms causing undesired bone loss following THA. It has been well established that the macrophages that absorb small particles of wear debris cytokinetically signal osteoclasts to resorb bone. The resultant osteolytic defect has the potential to compromise the surrounding host bone, leading to a variety of problems that can lead to possible surgical revision of the prosthesis. The surrounding bone’s ability to adjust to the altered mechanical demands (i.e. stress shielding) leads to additional undesired bone loss. Bisphosphonates have been shown to have a positive effect in some of these processes. (Stockley et al. 2001, Wang et al. 2003) Several studies indicate that bisphosphonates could prevent the periprosthetic bone loss after THA, but it is unclear if bisphosphonates prevent periprosthetic fractures. It is also uncertain whether bisphosphonates could affect on particle related osteolysis. (Bauer et al. 2002, Hamer et al. 2003, Hasselman et al. 1998, Jurvelin et al. 2002)

In a meta-analysis of the 14 RCTs available on the subject of bisphosphonates and periprosthetic bone loss, Lin and coworkers concluded that there is moderate evidence that both the short-term and middle-term effect of bisphosphonate use after arthroplasty is promising. This was also the conclusion in a more recent meta-analysis concluded by Shi et al. They stated that bisphosphonates significantly prevented the loss of periprosthetic bone mineral density at one year and more than five years after THA. Several studies indicate that the periprosthetic bone loss is minimal in the main load bearing areas of the proximal femurs with the use of bisphosphonates. This protective effect probably persists for 18 to 70 months after the end of bisphosphonate treatment. These RCTs did not address the clinically relevant outcomes, and thus more research in this field is needed. However there are a few studies that suggest that the use of bisphosphonates could indeed reduce the periprosthetic fracture risk. (Lin et al. 2012, Shetty et al. 2006, Shi et al. 2018, Trevisan et al. 2010)

It has been shown that bisphosphonates have positive effects on periprosthetic BMD and possibly also on clinical outcomes. Yet the optimal timing for initiation of
bisphosphonates in arthroplasty patients is unknown, especially to prevent periprosthetic changes during the early months after surgery. (Bhandari et al. 2005)

The positive effect of alendronate can also be seen in the knee after total knee arthroplasty. In a study carried out by Jaroma et al. the mean femoral metaphyseal BMD was significantly higher than in the control group after the administration of alendronate postoperatively. This effect seemed to last up to four years postoperatively. It has not yet been proven if this positive effect could be reduce periprosthetic fractures. (Jaroma et al. 2015)

Zolendronic acid is a long-lasting antiresorptive agent, and it has been widely used to treat high-risk osteoporotic patients. It has also been proven to reduce short-term periprosthetic bone loss. Aro and colleagues found that it also has a long-lasting, partially positive effect on periprosthetic bone loss despite the fact that the treatment did not enhance femoral stem stability or reduce less revision surgeries. (Aro et al. 2018, Bhandari et al. 2005)

There are also potential biological agents to increase bone formation. Parathyroid hormone (PTH) is an anabolic agent that can directly stimulate bone formation, and can increase BMD in patients with postmenopausal osteoporosis, decreasing the risk of fracture (Girotra et al. 2006). Indications for the use of teriparatide include postmenopausal women with osteoporosis at a high risk of fracture or those not responding well to bisphosphonates. Teriparatide increases BMD both in the lumbar spine and in the femoral neck area. It is still unclear if teriparatide could be used to preventing periprosthetic bone loss. (Body et al. 2002)

Also denosumab has been proven to prevent periprosthetic bone loss and even restore the decreased periprosthetic BMD near to normal levels. (Nagoya et al. 2018)

Calcitonin is an inhibitor of osteoclast bone resorption and has been an alternative to HRT or bisphosphonates for the treatment of osteoporosis, but it is no longer used anymore. The results on whether calcitonin can prevent periprosthetic bone loss are conflicting. (Arnala et al. 2012, Overgaard et al. 1996)

2.7 BONE HISTOMORPHOMETRY IN PATIENTS WITH OSTEOARTHRITIS

Bone is a living and metabolically active tissue, and it is constantly changing through resorption and regeneration. Bone structure is typically divided into the thick cortex and trabecular cancellous bone. The composite construction of bone form from an organic matrix i.e. osteoids and minerals, mainly calcium hydroxy apatite. Bone-resorbing osteoclasts and bone-forming osteoblasts are responsible for bone remodeling process.

In OA the cancellous bone mass and the strength of the bone seems to be higher in the proximal femur. Histologically, it has been shown that in OA bone formation and volume are increased in subchondral trabecular bone, with little resorption. The amount of osteoid and the cancellous bone thickness are also increased. The bone
mass is greater in those areas where the cartilage has suffered more. It seems that the more the cartilage is damaged, the deeper those subchondral bone changes can be seen. (Jordan et al. 2003) It has been speculated that primary OA is linked to extensive bone disease. Gevers et al. found that patients with hand OA had increased bone mass in the iliac crest than patients without OA. There are few studies investigating bone histomorphometry in OA patients. Gevers et al. suggested that there is a connection between hand OA and increased bone mass in the iliac crest. On the other hand, Fazzalari et al. suggested that the iliac crest is not useful to assess the bone changes in femoral OA. There are no studies investigating whether iliac crest or proximal femoral bone turnover is related to periprosthetic bone changes in OA patients. (Fazzarali et al. 1992, Gevers et al. 1989)

There is increasing evidence that the subchondral bone may contribute to the pathogenesis of OA, and that OA could affect bone structure and metabolism in general. Nonetheless, most studies focus mainly on cartilage degeneration and erosion, and skeletal changes are recognized only in the late stages (Zupan et al. 2013).
3 AIMS OF THE STUDY

The aims of the present study were:

1. To study long-term (up to 10 years postoperatively) periprosthetic BMD changes after THA. (study I)
2. To study short-term (one-year) periprosthetic BMD changes after HRA. (study II)
3. To find out if six months of alendronate treatment can prevent periprosthetic bone loss during long-term follow up after THA. (study III)
4. To study if bone turnover assessed by bone histomorphometry is associated with periprosthetic BMD changes. (study IV)
4 SUBJECTS AND METHODS

4.1 GENERAL STUDY DESIGN

The THA patients were operated on between 1993-1995. They belong to the PERIPROT-project (Kröger et al. 1996, Venesmaa et al. 2001). In the present study 38 patients were followed up to 10 years postoperatively with DXA measurements to show the long-term BMD changes after THA.

A further 26 patients underwent with hip resurfacing arthroplasty between 2003-2006 (HRA) and their periprosthetic BMD was measured one year postoperatively. The postoperative BMD measurements were made using custom-made regions of interest right under the prosthesis in the femoral neck area. The main goal of this study was to investigate if there was loss in the periprosthetic BMD or could HRA bypass the stress-shielding phenomenon.

A total of 16 THA patients were enrolled in a randomized controlled trial to study the effect of six months oral alendronate on periprosthetic BMD. All patients were followed-up to 5 years to assess the long-term effect of this drug.

Iliac crest and intertrochanteric bone biopsies were collected during the THA operation in 10 cases. We wanted to study if bone turnover correlates with periprosthetic bone mineral density changes.

The approval of the local ethics committee was sought and obtained for each study project.

4.1.1 Long term follow-up of periprosthetic bone density after THA (study I)

A total of 38 patients were enrolled in this prospective BMD study. They underwent either an uncemented primary THA (25 patients) or a cemented primary THA (13 patients) using the standard operative technique at Kuopio University Hospital in 1993–1995. At that time we used a protocol that for patients over 65 years of age a cemented prosthesis was preferably chosen and if the patient was below that age, an uncemented prosthesis was used. The operating surgeon had the opportunity to change the plan according to the patient needs and bone quality. For inclusion in this study, patients had to be without bone metabolic disease and not have taken any bone-affecting drugs previously or during the follow-up.

Femoral implants used in the operations were either one-third proximal porous-coated Bimetric titanium alloy (Ti6A14V; Biomet, Inc., Warsaw, IN, USA) or cobaltchrome Lubinus SPI stems with a collar (Waldemar Link CMBH&CD, Germany). A modern cementing technique was used with Palacos R-40 cum Gentamicin (contrast medium: zirconium; Schering-Plough, Brussels, Belgium).

The uncemented hips were allowed only partial weight bearing on the operated hip for six weeks after THA. Full weight bearing was reached gradually over the next
six weeks. The cemented hips were allowed full weight bearing immediately after surgery, although most patients used crutches temporarily.

The mean age at the time of operation of the uncemented group (n=25) was 58 (46–68) years and the BMI was 30.1 (23–34) kg/m^2. In the cemented group (n=13) the mean age was 69 (58–74) years and the BMI was 27 (21–34) kg/m^2. (Table 2)

Femoral BMD was measured with Lunar DPX or Lunar DPX-IQ densitometry (Lunar Corp., Madison, WI, USA). During scanning, the patient was placed in the supine position on the scan table. In each scan, the femur was kept in neutral rotation using standard knee and foot supports to minimize the measurement error. The scan window included the metallic implant, bone and soft tissues. The special orthopedic software version 1.2 (Lunar Corp.) was used. The software automatically excluded soft tissue and the metallic implant, and only the bone was measured. The bone mineral content (BMC), area (cm^2) and BMD (g/cm^2) were calculated in seven regions of interest (ROIs; Gruen Zones; Figure 3). BMD was measured laterally (zones 1, 2 and 3) and medially (zones 5, 6 and 7) around the stem and also at least 1 cm distally from the tip of the stem (zone 4). To measure the patient’s periprosthetic BMD on the non-operated side, the scan window was reflected to the contralateral side.

![Figure 3. The standard Gruen Zones used in these studies.](image)

Measurements were made post-operatively at 4–14 days and 3, 6, 12, 24, 36, 60 and 120 months after THA. Clinical and radiological evaluations were made at each visit. While the DXA scanner was changed from DPX to DPX-IQ during the study, 10 patients with hip arthroplasty were scanned with both instruments to establish a cross-calibration between the instruments. In each ROI, a high linear correlation was found for the BMD values obtained with DPX and DPX-IQ instruments. Because of the high linearity, a first order polynomial could be fitted into the data in each ROI to derive a correction for the BMD values with DPX-IQ. Using these best fit correction
equations, “DPX-compatible” BMD values were calculated for the DPX-IQ measurements.

4.1.2 BMD after hip resurfacing arthroplasty (study II)

For inclusion in this study, the patients had OA that could be operated using the HRA. The selected patients were relatively young and physically active. Most of the patients had grade two or three OA according to the Kellgren-Lawrence classification (13) (Grade two n=12, Grade three n=15 and Grade four n=1). Four different brands of prostheses were used since during the time of the study our clinical unit was testing these implants. A total of 26 patients (28 hips) received HRA either using the Birmingham hip resurfacing system (Smith & Nephew UK, London, UK.) (n=5), Conserve (plus) (Wright Medical Technology, Inc. Arlington, USA) (n=3), Cormet (Stryker, Kalamazoo, USA) (n=6) or Biomet re-cap (Biomet, Inc. Warsaw, Indiana, USA) (n=14).

The mean age was 55.2 (range 38–69) years at the time of the operation. We included 22 (24 hips, since two patients had both sides operated) men and 4 women on this study. The mean BMI was 27.8 (17.9–34.8) (Table 2.). The operation was performed using a posterolateral approach with a standard operative technique. The surgeon decided which prosthesis would be used in the operation. All the patients were allowed full weight bearing on the second post-operative day.

Clinical and radiological evaluations were made at each visit, and any adverse events were registered. Periprosthetic BMD was measured using the Lunar DPX-IQ DXA instruments (Lunar Corp., Madison, WI, USA). During scanning, the patient was placed in the supine position on the scan table. In each scan the femur was kept in neutral rotation using the standard knee and foot supports to minimize the measurement errors. The scan window included soft tissues, bone and the metallic implant. The special orthopedic software in use, version 1.2 (Lunar Corp.), automatically excluded soft tissues and the metallic implant from the analyses. Bone mineral content (BMC, g), areas (cm²), and BMD (g/cm²) were determined from four manually determined regions of interest postoperatively, at three months from surgery and at one year from surgery. The femoral neck was divided into four regions of interest (ROI). Area A is located superolaterally, B superomedially, C inferolaterally and D is inferomedially. The areas range from the prosthesis to the base of femoral neck (Figure 4). For analysis, we also combined the proximal and distal ROIs i.e. the proximal ROI included the original ROIs A and B and the distal ROI included C and D.
4.1.3 Alendronate treatment after THA (study III)

Sixteen patients participated in this prospective randomized controlled study. The study protocol was approved by the Ethics committee of Kuopio University’s Hospital and the patients provided a written informed consent. For inclusion into this study, the patients neither suffered from any diseases affecting bone metabolism nor used any bone-inducing medication previously. Moreover, the patients understood not to use other bone growth-inducing medications during the study. The patients also had to be able to comply with a standard postoperative mobilization schedule.

The patients were operated on from May, 1998 to October, 1999 using standard operative techniques in Kuopio University Hospital. Uncemented THA was performed using a hydroxyapatite-covered femoral stem and hydroxyapatite-coated cup (Omnifit; Osteonics, Stryker Howmedica, Allendale, NJ, USA). The indication for arthroplasty was primary hip OA in 15 patients. One patient was operated on to treat mild congenital luxation of the hip and acetabular dysplasia. Full weight bearing was allowed immediately after THA. However, all patients used crutches for 3 to 6 weeks after surgery.

The patients were randomized into two study groups, and they were followed up to five years. Nine (five men and four women) received only 500 mg calcium carbonate (Calcichew; Nycomed Pharma, Oslo, Norway) daily. Seven (two men and
five women) received 10 mg alendronate sodium (Fosamax; Merck, B. V. Haarlem, The Netherlands) supplemented by 500 mg calcium carbonate daily. Alendronate tablets were administrated orally 30 minutes before the breakfast, once a week beginning the first day after surgery. The duration of the treatment was 6 months. The mean age of the subjects was 58.9 years in the calcium-only group (range, 46 to 70 years) and 64.7 years in the alendronate-treated group (range, 59 to 71 years). All women were postmenopausal. The mean body mass index (BMI) was 27.8 kg/m² in the calcium-only group (range, 22.3 to 44.3 kg/m²) and 28.5 kg/m² in the alendronate-treated group (range, 23.0 to 36.2 kg/m²). (Table 2.)

Periprosthetic BMD was measured using the Lunar DPX or Lunar DPX-IQ DXA instruments (Lunar Corp., Madison, WI, USA). Although two different pencil-beam DXA-models were in use, importantly, the measurements for each patient were performed using the same machine during the follow-up. The measurements were all done with no knowledge of the patients’ treatment protocol. During scanning, the patient was placed in the supine position on the scan table. In each scan the femur was kept in neutral rotation using standard knee and foot supports to minimize the measurement errors. The scan window included soft tissues, bone and the metallic implant. The special orthopedic software in use, versions 1.2 and 4.6d (Lunar Corp.), automatically excluded soft tissues and the metallic implant from the analyses.

Bone mineral content (BMC, g), areas (cm²), and BMD (g/cm²) were determined from seven regions of interest (ROIs; zones 1 through 7) based on Gruen zones. In addition, zones 1 through 7 were combined to represent the total ROI measurement (totROI), and zones 1 and 7 were combined to represent the proximal femoral ROI measurement (prROI). Postoperative BMD measurements were made within two weeks of THA, i.e. at that time it was possible to achieve optimal positioning of the hip, and subsequently at 3, 6, 12, 24, 36 and 60 months (the mean follow-up time was 59.6 months, SD 2.4 months). Clinical and radiological evaluations were made at each visit, and any adverse events were registered.

4.1.4 Bone histomorphometric findings in patients with hip osteoarthritis (study IV)

Samples from the proximal femur and the iliac crest were collected from ten patients (five men and five women) suffering OA and undergoing THA in the years 1993-1995. The total number of collected samples was 74 but we chose only ten samples for this study because those samples were best preserved and could be still measured accurately. The mean age of male patients at the time of surgery was 61.5 (SD 5.0) years and in female patients was 65.2 (SD 1.2) years respectively. All of the men had an uncemented prosthesis and three women had an uncemented and two cemented prosthesis. The study characteristics can be found in table 2.

The iliac crest bone sample was taken perpendicular to the iliac crest 2cm behind the anterosuperior iliac spine. The trochanteric sample was taken right after removing the femoral head from the cut trochanteric area. Bone samples were crafted by extracting water out of the sample using an ethanol solution. They were then
embedded in methylmetacrylate. 5 µm thick slices were cut and attached to the sampleglass using Haupt-solution. Masson Goldner trichome-stained and native cuts were analyzed (Figure 5).

Figure 5. Biopsy-samples from the proximal femur (on the left) and from the iliac crest (on the right).

Bone sections were analysed with bright light microscopy using a magnification of X200. The main parameters assessed were bone volume (BV/Tissue Volume, %), including both mineralized and unmineralized bone volumes. Osteoid surfaces (OS/Bone Surface, %), osteoid volume (OV/BV, %) and osteoid thickness (O.Th, µm) were measured. Eroded surfaces (ES/Bone Surface, %) were also determined. Bone cells, i.e. osteoblasts and osteoclasts, on trabecular surfaces were measured (Ob.S/BS, %; Oc.S/BS, %).

A repeatability measurement was also conducted to double-check the measurement method. Altogether four samples were analyzed and compared previous measurements made by a senior researcher. The best repeatability was in the measurements of bone volume and tissue volume. Erosion and osteoclast parameters were less repeatable, which could be due to the small amount of resorption and osteoclasts of the samples.

4.2 STATISTICAL ANALYSIS

In the three first studies postoperative BMD changes were calculated by normalizing the BMD values to the immediate postoperative BMD. Any change was expressed as a percentage (%). We used SPSS software, version 14.0 (SPSS Inc., Chicago, Il, USA). Friedman’s test was applied to test the statistical significance of BMD changes during follow-up within the groups. The linear correlations of the periprosthetic BMD change with selected factors (age, sex, BMI, fixation type) were also studied. All tests were 2-tailed, using a critical p value of 0.05.

In the fourth study statistical analyses were performed using SPSS software (version 20.0; SPSS, BM Corp., Armonk, N.Y., USA). Pearson’s linear correlation coefficients were calculated between the BMD and bone histomorphometric parameters.
### Characteristics of the study subjects (studies I-IV)

<table>
<thead>
<tr>
<th>STUDY I</th>
<th>Cemented</th>
<th>Uncemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>2/11</td>
<td>13/12</td>
</tr>
<tr>
<td>Age (year)</td>
<td>69 (58-74)</td>
<td>58 (46-68)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (31-34)</td>
<td>30.1 (23-34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY II</th>
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</tr>
</thead>
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<tr>
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<tr>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 (17.9-34.8)</td>
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<table>
<thead>
<tr>
<th>STUDY III</th>
<th>Calcium only group</th>
<th>Alendronate treated group</th>
</tr>
</thead>
<tbody>
<tr>
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<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Sex (male/female)</td>
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<td>2/5</td>
</tr>
<tr>
<td>Age (year)</td>
<td>59 (46-70)</td>
<td>65 (59-71)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 (22.3-44.3)</td>
<td>28.5 (23.0-36.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY IV</th>
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<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5</td>
</tr>
<tr>
<td>Age (year)</td>
<td>61.5 (SD 5.0)</td>
<td>65.2 (SD 1.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>29.8</td>
</tr>
<tr>
<td>Femur fixation type</td>
<td>Uncemented 5</td>
<td>Uncemented 3/Cemented 2</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of the study subjects in all of the studies (I-IV).
5 RESULTS

5.1 BONE MINERAL DENSITY AFTER THA, A 10-YEAR FOLLOW-UP STUDY (I)

During the first post-operative year, BMD decreased significantly in both groups mainly in the calcar area. The decrease in zone 7 in the uncemented group was 21.9% (p<0.005) and 26.1% in the cemented group (p<0.005). After that, BMD changes were minimal up to ten years, only a few percentages in different ROIs (Table 3). The main decrease at the end of the follow-up was still in the calcar area, with uncemented at 31.1% (p<0.001) and cemented at 38.7% (p<0.01; Wilcoxon test).

When the uncemented prosthesis was compared with the cemented prosthesis, few statistically significant differences in BMD values were found, and most of them were in zone 3. Zones 1 and 7 were combined to form the proximal ROI and zones 3 and 5 to form the distal ROI. At the end of the follow-up, both groups showed a slight continuous BMD loss in the proximal part of the femur and a slight increase in the distal part of femur, especially after uncemented THA. The changes did not reach statistical significance. The total BMD of the contralateral side showed a minimal but statistically significant bone loss during the entire 10-year follow-up period (0.9%, p=0.003). (Figure 6.)
Table 3. The absolute BMD values during the ten year follow-up time in uncemented and cemented groups. Percentual changes from the postoperative values can be seen in the end of each row.

### BMD (SD)-Uncemented

<table>
<thead>
<tr>
<th></th>
<th>Postop</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>60 months</th>
<th>120 months</th>
<th>%-change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruen1</td>
<td>0.96 (0.21)</td>
<td>0.87 (0.24)</td>
<td>0.86 (0.27)</td>
<td>0.87 (0.27)</td>
<td>0.89 (0.28)</td>
<td>0.85 (0.30)</td>
<td>0.82 (0.31)</td>
<td>0.80 (0.25)</td>
<td>-17.0 %</td>
</tr>
<tr>
<td>Gruen2</td>
<td>1.76 (0.26)</td>
<td>1.63 (0.30)</td>
<td>1.59 (0.32)</td>
<td>1.61 (0.31)</td>
<td>1.61 (0.30)</td>
<td>1.60 (0.31)</td>
<td>1.61 (0.39)</td>
<td>1.63 (0.40)</td>
<td>-7.4 %</td>
</tr>
<tr>
<td>Gruen3</td>
<td>1.92 (0.24)</td>
<td>1.82 (0.29)</td>
<td>1.83 (0.27)</td>
<td>1.86 (0.27)</td>
<td>1.87 (0.30)</td>
<td>1.87 (0.31)</td>
<td>1.87 (0.32)</td>
<td>1.90 (0.41)</td>
<td>-1.1 %</td>
</tr>
<tr>
<td>Gruen4</td>
<td>1.79 (0.25)</td>
<td>1.70 (0.26)</td>
<td>1.70 (0.26)</td>
<td>1.69 (0.27)</td>
<td>1.72 (0.29)</td>
<td>1.72 (0.29)</td>
<td>1.69 (0.30)</td>
<td>1.87 (0.53)</td>
<td>4.5 %</td>
</tr>
<tr>
<td>Gruen5</td>
<td>1.85 (0.24)</td>
<td>1.77 (0.31)</td>
<td>1.80 (0.28)</td>
<td>1.80 (0.28)</td>
<td>1.83 (0.31)</td>
<td>1.82 (0.31)</td>
<td>1.86 (0.31)</td>
<td>1.95 (0.40)</td>
<td>5.4 %</td>
</tr>
<tr>
<td>Gruen6</td>
<td>1.60 (0.27)</td>
<td>1.47 (0.28)</td>
<td>1.45 (0.30)</td>
<td>1.43 (0.31)</td>
<td>1.43 (0.31)</td>
<td>1.43 (0.29)</td>
<td>1.45 (0.29)</td>
<td>1.46 (0.36)</td>
<td>-8.7 %</td>
</tr>
<tr>
<td>Gruen7</td>
<td>1.19 (0.24)</td>
<td>1.02 (0.24)</td>
<td>0.99 (0.28)</td>
<td>0.93 (0.27)</td>
<td>0.93 (0.27)</td>
<td>0.93 (0.33)</td>
<td>0.88 (0.35)</td>
<td>0.82 (0.36)</td>
<td>-31.1 %</td>
</tr>
</tbody>
</table>

### BMD (SD)-Cemented

<table>
<thead>
<tr>
<th></th>
<th>Postop</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>60 months</th>
<th>120 months</th>
<th>%-change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruen1</td>
<td>1.01 (0.14)</td>
<td>0.92 (0.15)</td>
<td>0.90 (0.13)</td>
<td>0.99 (0.29)</td>
<td>0.91 (0.19)</td>
<td>0.89 (0.19)</td>
<td>0.87 (16)</td>
<td>0.82 (0.17)</td>
<td>-18.8 %</td>
</tr>
<tr>
<td>Gruen2</td>
<td>1.71 (0.16)</td>
<td>1.56 (0.26)</td>
<td>1.50 (0.31)</td>
<td>1.50 (0.31)</td>
<td>1.48 (0.36)</td>
<td>1.48 (0.35)</td>
<td>1.50 (0.39)</td>
<td>1.42 (0.41)</td>
<td>-17.0 %</td>
</tr>
<tr>
<td>Gruen3</td>
<td>1.72 (0.20)</td>
<td>1.59 (0.27)</td>
<td>1.57 (0.29)</td>
<td>1.58 (0.28)</td>
<td>1.58 (0.29)</td>
<td>1.59 (0.30)</td>
<td>1.64 (0.34)</td>
<td>1.58 (0.35)</td>
<td>-8.1 %</td>
</tr>
<tr>
<td>Gruen4</td>
<td>1.82 (0.23)</td>
<td>1.72 (0.25)</td>
<td>1.72 (0.23)</td>
<td>1.73 (0.24)</td>
<td>1.73 (0.25)</td>
<td>1.65 (0.27)</td>
<td>1.78 (0.30)</td>
<td>1.82 (0.23)</td>
<td>0.0 %</td>
</tr>
<tr>
<td>Gruen5</td>
<td>1.69 (0.20)</td>
<td>1.61 (0.24)</td>
<td>1.61 (0.26)</td>
<td>1.62 (0.27)</td>
<td>1.61 (0.28)</td>
<td>1.62 (0.27)</td>
<td>1.68 (0.32)</td>
<td>1.63 (0.32)</td>
<td>-3.6 %</td>
</tr>
<tr>
<td>Gruen6</td>
<td>1.61 (0.20)</td>
<td>1.42 (0.27)</td>
<td>1.37 (0.26)</td>
<td>1.35 (0.29)</td>
<td>1.34 (0.32)</td>
<td>1.32 (0.31)</td>
<td>1.36 (0.35)</td>
<td>1.20 (0.33)</td>
<td>-25.5 %</td>
</tr>
<tr>
<td>Gruen7</td>
<td>1.11 (0.18)</td>
<td>0.92 (0.23)</td>
<td>0.87 (0.23)</td>
<td>0.82 (0.23)</td>
<td>0.79 (0.20)</td>
<td>0.78 (0.24)</td>
<td>0.83 (0.22)</td>
<td>0.68 (0.21)</td>
<td>-38.7 %</td>
</tr>
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</table>
We also compared BMDs in both groups to control side BMDs (non-operated) ten years after surgery. In the cemented group most of the Gruen zones showed significant bone loss compared to the control side (Table 4). The percentage of BMD changes varied from zone 1 to zone 7: -5.7%, -17.4%, -14.1%, +2.2%, -12.4%, -27.3% and -44.3%. In the uncemented group there were also significant changes, although the bone loss percentage was not as extensive. Percentage changes in BMD were (from zone 1 to zone 7): -8.0%, -5.2%, +3.3%, +5.1%, +4.8%, -11.5% and -32.8% respectively.

![Table 4. The BMD-measurements from the operated side compared to the control side.](image)
There were no immediate post-operative complications, and all patients recovered fully without any major complications during the 10-year follow-up period. We went through all the patient charts and records from our patient data system from surgery up to year 2014 and there were no signs or symptoms showing femoral loosening within the study groups. After 10 years, six patients (four from the uncemented and two from the cemented group) went through an acetabular component revision, mostly due to wearing or osteolysis below the acetabular component. One patient was re-operated on due to recurrent luxation, but this patient’s BMD values did not differ significantly from the others.

Figure 6. Combined proximal ROIs (Gruen 1+7) and distal ROIs (Gruen 3+5) and percentual values of the BMD in patients with uncemented and cemented femoral implants during 10 years of follow-up.
5.2 BONE MINERAL DENSITY AFTER HIP RESURFACING ARTHROPLASTY (II)

There were no postoperative complications, and all patients recovered without complications. The absolute and BMD values and percentual changes are shown in Table 5. Within three months of follow-up BMD decreased in three ROIs and increased in one ROI. In ROI A the increase was 1.9%, and in B the decrease was 1.5%, in C 5.2% and in D 2.7% respectively. At one year of follow-up 3 out of 4 ROIs showed a slight BMD increase. There were 1.1%, 5.4% and 1.3% increases in ROIs A, B and D, respectively. ROI C showed a 3.9% decrease at the one-year follow-up. In the proximal ROI (A + B) there was a 0.6% BMD decrease at 3 months postoperatively, but at the one-year measurement the proximal part showed a 4.5% increase. In the distal ROI (C + D) there was a 4.4% and 0.7% BMD decrease at 3 months and 1 year, respectively. All the changes were statistically non-significant (NS).

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Postoperative</th>
<th>3 months</th>
<th>12 months</th>
<th>P-value</th>
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<tbody>
<tr>
<td>A</td>
<td>1.13(0.32)</td>
<td>1.13(0.36)</td>
<td>1.16(0.27)</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>0.89(0.21)</td>
<td>0.88(0.30)</td>
<td>0.96(0.22)</td>
<td>NS</td>
</tr>
<tr>
<td>C</td>
<td>1.52(0.32)</td>
<td>1.44(0.36)</td>
<td>1.46(0.26)</td>
<td>NS</td>
</tr>
<tr>
<td>D</td>
<td>1.37(0.25)</td>
<td>1.33(0.28)</td>
<td>1.41(0.29)</td>
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</table>

NS = Not significant

<table>
<thead>
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<th>Region of interest</th>
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<th>3 months</th>
<th>12 months</th>
<th>P-value</th>
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<tr>
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</tr>
<tr>
<td>C</td>
<td>100</td>
<td>94.5</td>
<td>95.5</td>
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<tr>
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<td>100</td>
<td>97.0</td>
<td>103.4</td>
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Table 5. The absolute and percentual values of the BMD after HRA during one year follow-up time.
5.3 THE EFFECT OF ALENDRONATE ON THE PERIPROSTHETIC BONE LOSS AFTER THA (III)

There were no postoperative complications during the follow-up, and no adverse events caused by the drugs were reported. No radiographic evidence of aseptic loosening was seen in any of the patients during the follow-up. There were no significant differences in age, BMI or sex distribution between the groups. The immediate postoperative BMDs were not significantly different between the study groups. During the 5 years of follow-up, the calcium-only group showed BMD variations ranging from a 48.4% decrease to a 1.9% increase. In the alendronate-treated group, the BMD changes varied from a 13.7% decrease to 7.9% increase. In the calcium group, the mean 5-year BMD decrease was 23.1% (SD 14.6) in BMD for prROI and 9.6% (SD 14.9) for totROI at the end of follow-up. In the alendronate group the decreases were smaller, 13.6% (SD 19.0) and 3.9% (SD 7.6) respectively. However, the changes between the study groups were not statistically different (Mann-Whitney test; Table 6 and 7 and Figure 7). There was a significant change between groups after 6 months of follow up, but subsequently the bone loss rates were quite similar. We also studied the influence of patients’ age, BMI and stem size on periprosthetic BMD changes. No significant correlations were found.
<table>
<thead>
<tr>
<th></th>
<th>prROI</th>
<th></th>
<th></th>
<th>p value 0-6 mo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p value 0-5 y&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-only</td>
<td>-14.26</td>
<td>-23.10</td>
<td>0.023</td>
<td>NS</td>
<td>NS</td>
<td>0.01</td>
</tr>
<tr>
<td>Alendronate</td>
<td>0.14</td>
<td>-13.55</td>
<td>0.023</td>
<td>NS</td>
<td>NS</td>
<td>0.05</td>
</tr>
<tr>
<td>totROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-only</td>
<td>-8.10</td>
<td>-9.60</td>
<td>0.023</td>
<td>NS</td>
<td>NS</td>
<td>0.004</td>
</tr>
<tr>
<td>Alendronate</td>
<td>-2.39</td>
<td>-3.90</td>
<td>0.023</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>b</sup> Mann-Whitney test
<sup>c</sup> Friedman test
Table 7. The mean periprosthetic BMD (SD) in the Calcium-only and Alendronate-treated groups during the 5-year follow-up time.

| Gruen Zone | Calcium-only group (n = 9) | | | | | | Alendronate-treated group (n = 7) | | | | | |
|------------|---------------------------|----------------|----------------|----------------|-----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
|            | Postoperative | 6 months | 5-years | p value<sup>a</sup> | Postoperative | 6-months | 5-years | p value<sup>a</sup> | Postoperative | 6-months | 5-years | p value<sup>a</sup> |
| 1          | 0.95 (0.17)   | 0.85 (0.18) | 0.80 (0.26) | NS             | 0.93 (0.24)   | 0.96 (0.19) | 0.91 (0.22) | NS             |                |                |                |                |
| 2          | 1.89 (0.20)   | 1.64 (0.41) | 1.64 (0.48) | 0.045           | 1.81 (0.25)   | 1.72 (0.32) | 1.72 (0.29) | NS             |                |                |                |                |
| 3          | 2.02 (0.27)   | 1.94 (0.35) | 1.91 (0.49) | NS             | 1.86 (0.35)   | 1.81 (0.36) | 1.84 (0.37) | NS             |                |                |                |                |
| 4          | 1.81 (0.26)   | 1.74 (0.28) | 1.71 (0.41) | NS             | 1.72 (0.34)   | 1.67 (0.35) | 1.67 (0.40) | NS             |                |                |                |                |
| 5          | 2.00 (0.25)   | 1.92 (0.27) | 1.98 (0.38) | NS             | 1.88 (0.26)   | 1.85 (0.22) | 1.88 (0.28) | NS             |                |                |                |                |
| 6          | 1.55 (0.30)   | 1.43 (0.30) | 1.45 (0.38) | NS             | 1.56 (0.08)   | 1.54 (0.21) | 1.58 (0.18) | NS             |                |                |                |                |
| 7          | 1.10 (0.15)   | 0.91 (0.16) | 0.79 (0.22) | 0.00           | 1.17 (0.26)   | 1.12 (0.34) | 0.98 (0.35) | 0.02           |                |                |                |                |
| totROI     | 1.62 (0.17)   | 1.49 (0.21) | 1.47 (0.32) | 0.004          | 1.56 (0.23)   | 1.52 (0.25) | 1.50 (0.27) | NS             |                |                |                |                |
| prROI      | 1.02 (0.13)   | 0.88 (0.15) | 0.79 (0.23) | 0.001          | 1.05 (0.24)   | 1.04 (0.24) | 0.90 (0.25) | 0.05           |                |                |                |                |

<sup>a</sup>Friedman's test  
NS = Not Significant
Figure 7. The mean percentual BMD change (with SD) in total and proximal regions of interest for 0, 6 months, 12 months, 36 months and 60 months follow-up time. Gray lines represent changes in the alendronate-treated group and black lines in the calcium-only group. The changes are significant within the study groups after 60 months follow-up time (p<0.05, Friedman’s test). The changes between the study groups were not significant.
5.4 BONE HISTOMORPHOMETRIC FINDINGS IN PATIENTS WITH HIP OSTEOARTHRITIS (IV)

The bone histomorphometric parameters were compared to the BMD changes in seven standard Gruen zones postoperatively at one and two year after THA. We found a statistically significant correlation between periprosthetic BMD changes in Gruen zone 7 and trabecular bone volume in both the iliac crest and proximal femur. These changes were evident both at the one-year and two-year follow-up. Other Gruen zones did not show statistically significant correlations. In terms of other bone turnover parameters we did not found any statistically significant correlations with the BMD changes (Table 8).

<table>
<thead>
<tr>
<th>Prox femur</th>
<th>BMD change 1 year postoperatively</th>
<th>Pearson correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV %</td>
<td>12.67 (6.31)</td>
<td>0.708 (p&lt;0.05)</td>
</tr>
<tr>
<td>OV/BV %</td>
<td>0.64 (0.72)</td>
<td>-0.351 (NS)</td>
</tr>
<tr>
<td>OS/BS %</td>
<td>5.62 (5.60)</td>
<td>-0.252 (NS)</td>
</tr>
<tr>
<td>ES/BS %</td>
<td>3.08 (1.64)</td>
<td>-0.335 (NS)</td>
</tr>
<tr>
<td>Ob. S/BS%</td>
<td>2.39 (5.60)</td>
<td>-0.265 (NS)</td>
</tr>
<tr>
<td>Oc. S/BS</td>
<td>0.38 (0.00)</td>
<td>0.206 (NS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prox femur</th>
<th>BMD change 2 years postoperatively</th>
<th>Pearson correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV %</td>
<td>12.67 (6.31)</td>
<td>0.799 (p&lt;0.05)</td>
</tr>
<tr>
<td>OV/BV %</td>
<td>0.64 (0.72)</td>
<td>-0.576 (NS)</td>
</tr>
<tr>
<td>OS/BS %</td>
<td>5.62 (5.60)</td>
<td>-0.427 (NS)</td>
</tr>
<tr>
<td>ES/BS %</td>
<td>3.08 (1.64)</td>
<td>-0.16 (NS)</td>
</tr>
<tr>
<td>Ob. S/BS%</td>
<td>2.39 (5.60)</td>
<td>-0.419 (NS)</td>
</tr>
<tr>
<td>Oc. S/BS</td>
<td>0.38 (0.00)</td>
<td>0.343 (NS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iliac crest</th>
<th>BMD change 1 year postoperatively</th>
<th>Pearson correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/IV %</td>
<td>13.3 (5.81)</td>
<td>0.836 (p&lt;0.05)</td>
</tr>
<tr>
<td>OV/BV %</td>
<td>1.05 (0.00)</td>
<td>0.212 (NS)</td>
</tr>
<tr>
<td>OS/BS %</td>
<td>6.81 (4.76)</td>
<td>0.070 (NS)</td>
</tr>
<tr>
<td>ES/BS %</td>
<td>5.21 (2.06)</td>
<td>0.147 (NS)</td>
</tr>
<tr>
<td>Ob. S/BS%</td>
<td>1.59 (1.54)</td>
<td>0.508 (NS)</td>
</tr>
<tr>
<td>Oc. S/BS</td>
<td>0.63 (0.05)</td>
<td>-0.123 (NS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iliac crest</th>
<th>BMD change 2 years postoperatively</th>
<th>Pearson correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/IV %</td>
<td>13.3 (5.81)</td>
<td>0.816 (p&lt;0.05)</td>
</tr>
<tr>
<td>OV/BV %</td>
<td>1.05 (0.00)</td>
<td>0.091 (NS)</td>
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<tr>
<td>OS/BS %</td>
<td>6.81 (4.76)</td>
<td>-0.064 (NS)</td>
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<tr>
<td>ES/BS %</td>
<td>5.21 (2.06)</td>
<td>-0.039 (NS)</td>
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<td>Ob. S/BS%</td>
<td>1.59 (1.54)</td>
<td>0.367 (NS)</td>
</tr>
<tr>
<td>Oc. S/BS</td>
<td>0.63 (0.05)</td>
<td>-0.216 (NS)</td>
</tr>
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</table>

Table 8. The bone histomorphometric measurements compared to the BMD change in Gruen zone 7 and the equivalent Pearson correlations and significance one and two years postoperatively.
6 DISCUSSION

6.1 GENERAL DISCUSSION

Hip arthroplasty is one of the most remarkable interventions in the field of surgery. The development of hip arthroplastic surgery in the 20th and 21st century and continuing new innovations has led to innumerable publications and vast knowledge about hip surgery. The fundamental goal of hip arthroplasty still remains the same: restoration of anatomy and biomechanics. Over one million primary and revision hip arthroplasties are performed worldwide annually, and operations are performed in more active and younger patients than ever before (Pivec et al. 2012).

The stress shielding concept was originally developed by Wolff back in 1892, and it still plays a role in understanding implant osteointegration and long-term survival. Postoperative BMD loss around the implant is a well-documented phenomenon and is partly associated with stress shielding. By understanding this phenomenon, it is possible to study if postoperative BMD loss could be reduced by implant design or medication (Sumner et al. 2015, Shi et al. 2018).

However, postoperative BMD loss is not only due to stress shielding. Numerous other factors affect bone remodeling after hip arthroplasty. For example, HRA was once thought superior in terms of periprosthetic bone loss, but because of other implant-related serious adverse events the use of HRA has ceased entirely in Finland. (Dunbar et al. 2014)

6.2 GENERAL DISCUSSION OF THE STUDY DESIGN

THA has good to excellent outcome when treating patients with end-stage OA. The results of THA are long lasting and the complication rates are tolerable. HRA gained popularity among orthopedic surgeons to treat young and active patients with OA. After severe adverse events connected to the MoM bearing arose, however, the use of HRA decreased dramatically. (Dunbar et al. 2014, Learnmonth et al. 2011)

DXA has been proven to be a precise and noninvasive method to investigate BMD after hip arthroplasty. It is broadly used, and measurements are easily comparable. Bisphosphonates are relatively safe drugs and are widely used to treat osteoporosis. Several studies indicate that bisphosphonates could be used to prevent periprosthetic bone loss and thus decrease the amount of bone loss associated complications. (Bhandari et al. 2005, Kröger et al. 1996, Venesmaa et al. 2001)

Bone histomorphometry is an accurate way to define bone quality and study bone turnover. (Tong et al. 2015)

All the patients in these studies were of a typical age for undergoing hip replacement as compared to the Finnish Arthroplasty Register. The inclusion criteria used made the study population homogenous. Patients with diseases and medications known to have an influence on bone metabolism were excluded from
these studies, and all the females had reached their physiological menopause. The subjects represent a reasonable sample population to investigate BMD changes around a hip prosthesis.

The study population in all of our studies is relatively small, and thus the statistical power is low. Also, in the HRA study most of the patients are young and active males, and this can cause a bias to the results. But when compared to the other studies in the field of periprosthetic bone mineral changes after hip arthroplasty the number of patients is quite similar.

No previous studies comparing bone histomorphometric parameters and periprosthetic bone changes exist. We were nonetheless able to find some statistically significant changes in our studies despite the small number of patients. (Hamer et al. 2003)

6.3 LONG-TERM PERIPROSTHETIC BONE LOSS AFTER THA

After the initial implantation of the prosthesis into the femur a series of events that cause significant BMD changes in the host bone is initiated. The changes are multifactorial, but the main reasons for this phenomenon are thought to be stress shielding, the initial surgical trauma, immobilization and wear of prosthetic materials that induce a complex biological response. Periprosthetic bone loss can lead to serious complications, such as aseptic implant loosening and periprosthetic fractures. These complications usually lead to revision surgery, which could be more demanding in the case of notable bone loss. Thus, it is important to understand and investigate periprosthetic bone loss after THA.

Cook et al. reported that 0.8% of patients at five years and 3.5% at ten years suffered a periprosthetic fracture caused by periprosthetic bone loss. In addition, in a more recent register study from Sweden the periprosthetic fracture rate within two years postoperatively was 0.4-0.6%. Furthermore in a Norwegian register study 3-10% of patients had aseptic loosening after 15 years follow-up. In Finland, according to the national arthroplasty register up to 11.7% of hip revision surgeries were carried out because of aseptic loosening of the acetabular component, up to 4.1% because of aseptic loosening of the femoral component, 0.5% because of primary cup instability and 0.9% because of primary femur instability. Evans and coworkers reported that based on different joint replacement registries the 25-year pooled survival of the hip replacements is around 58%. (Cook et al. 2008, Evans et al. 2019, Furnes et al. 2001, Hailer et al. 2010, Finnish Arthroplasty Register, www.thl.fi/far)

The previous studies by Venesmaa (2001), Decking (2008) and Marchetti (1996) have shown that most of the periprosthetic bone loss occurs in the first postoperative year and the bone loss is more prominent in the proximal calcar area. It is speculated that most of these changes in the BMD are because of stress shielding. The average bone loss in the proximal femur may be as great as 28% during the first 12 months after surgery. We also know from large register studies that most of the complications and revision surgeries due to complications happen in the first postoperative year.
The leading causes for revisions are instability of the hip and infections. The majority of the early periprosthetic fractures are because of the forceful initial surgical work (i.e. broaching the femoral canal and introduction of the femoral prosthesis). After five years postoperatively the leading cause for a major revision surgery is aseptic loosening of the implant. Most of these aseptic loosenings happen in the acetabular component (Ulrich et al. 2008). While there is no existing data or studies indicating that periprosthetic BMD changes are actually the cause of the implant failure, there may be an association between these two events. Ulrich et al. (2008) also showed that most of the periprosthetic fractures occurred in the first five postoperative years. There is obviously a strong link between poor bone quality and late fractures. It seems that periprosthetic bone loss after THA may play a role in terms of the implant survival.

Not all femoral implants act similarly. The more anatomic the prosthesis is the less BMD loss can be seen after THA, probably because of less stress shielding (Huiskes et al. 1992). The fixation type of the implant seems also have an effect to the postoperative BMD, but these results are somewhat conflicting. Chandran et al. (2012) conducted a study where they compared bone remodeling around the implant in both cemented and uncemented hip arthroplasties and extended their study up to twelve years postoperatively. In their study the periprosthetic BMD seemed to be better preserved around the uncemented prosthesis than around the cemented one. Comparison of clinical parameters showed no significant difference. We found in our study that there were some minimal differences in the changes in BMD between cemented and uncemented prostheses, but these changes were not statistically significant.

Several studies have shown that there are great changes in BMD in the first postoperative year but after that, a plateau is reached. In our study the BMD decrease one year after THA was 21.9% in Gruen zone 7 in the uncemented group and 26.1% in the cemented group. We also found that the annual periprosthetic bone loss was only few percentages after the first year. The results of our study are similar to other studies with a long-term follow up (Chandran et al. 2012, Merle et al. 2011, Nysted et al. 2011, Steens et al. 2008). These findings and correlations with clinical parameters raise the question, what is the importance of stress shielding-related bone loss to femoral implant loosening five years postoperatively, if the periprosthetic bone loss around the implant has reached a plateau stage. Aro and coworkers managed to show that despite the well documented early BMD loss, anatomically designed femoral stems showed good stability up to nine years when evaluated with radiostereometric analysis and radiographs (Aro et al. 2018). Probably the biologic inflammatory response to the debris caused by the wear of the prosthesis is a more important reason for aseptic loosening of the implant. Why the aseptic loosening of the acetabular component is more frequent than aseptic loosening of the femoral component is also unclear. Especially particle-related osteolysis causes loosening of the acetabular cup, however, and also leads to osteolysis in the trochanteric area.
contrast, because the femoral stem is osteointegrated distally, it stays stable. (Kurcz et al. 2018)

Periprosthetic bone loss after THA is significant during the first year after surgery, and the main reason for this seems to be the stress-shielding phenomenon. After that the bone loss is less and merely reflects the normal aging process. The significance of periprosthetic bone loss regarding prosthetic survival is unclear.

6.4 PERIPROSTHETIC BONE LOSS AFTER HIP RESURFACING ARTHROPLASTY

One of the reasons used to rationalize HRA was the fact that it preserved femoral bone, especially in the proximal femur, which is most affected by periprosthetic bone loss. This was once thought to lead to easier revisions when needed. HRA facilitates more physiological weight distribution and thus higher mechanical loading to the proximal femoral area. It has been shown in many studies that the HRA actually preserves the bone better than THA. Gerhardt et al. (2015) proved that there is also a small increase in BMD after HRA in the femoral neck. In their study the BMD showed 7% increase in the calcar area one year after HRA. The overall BMD changes in the proximal femur was 0.1-4.1% and after the first postoperative year these changes remained stable. We had similar findings in our study. Within one year after surgery the BMD changes in our custom-made regions of interest in the femoral neck area showed a slight increase. In terms of BMD and bone preservation the HRA seems to be a better option than conventional THA, but other problems and adverse events limited or even discontinued the use of HRA entirely.

Despite the fact that HRA seems to preserve BMD and even increase the periprosthetic bone mass these changes have not been proven clinically relevant. As Dunbar et al. (2014) and Amstutz et al. (2015) have reported that because of the numerous adverse events and complications related to HRA and especially to the MoM bearing, the use of this type of implant is no longer justified. Dunbar also showed that unlike what was thought before, HRA does not lead to easier revisions nor does it have a more acceptable revision rate. (Amstutz et al. 2015, Dunbar et al. 2014)

6.5 EFFECT OF ALENDRONATE ON PERIPROSTHETIC BONE LOSS

Since its first introduction in the 1990s alendronate has proven to be a relatively safe and effective treatment for patients suffering from osteoporosis. Alendronate inhibits osteoclast-mediated bone resorption and thus prevents bone loss. Alendronate reduces the risk of fractures in the hip, spine and wrist by almost 50% compared to placebo (Black et al. 1996). However, alendronate can also have a negative effect on bone, causing atypical femoral fractures (Lenart et al. 2008).
Many studies have shown that the periprosthetic bone mass decreases after hip replacement surgery. It has been speculated that bone loss may lead to devastating complications such as aseptic loosening and periprosthetic fractures. Since bisphosphonates (e.g. alendronate) have been proven to preserve and increase bone mass in osteoporotic patients, several studies have been conducted to study if the same positive effect can be seen after hip replacement surgery.

In a meta-analysis, Lin et al. (2012) collected 14 RCTs to analyze the effect of bisphosphonates on periprosthetic bone loss. There were over 600 patients involved in this meta-analysis and the mean follow-up time was approximately five years. Their primary finding was that bisphosphonates significantly reduced periprosthetic bone loss not only in the first postoperative year but also in the mid-term follow-up time. The effect lasted more than 18 months after discontinuation of the bisphosphonates. The most prominent effect was in the first three months after the index surgery and one year after surgery suggesting that bisphosphonates have a positive effect both on early bone resorption caused by iatrogenic damage and the late stress shielding and debris-induced osteolysis, respectively. Our findings in the alendronate study are similar to this, and actually our study was included in this meta-analysis. We managed to show in our study that in the alendronate-treated group the amount of bone loss was significantly less than in the calcium-only group and this effect was best seen in the proximal part of the femur. It is, however, yet unclear if the administration of postoperative bisphosphonates could have a clinical relevance.

As suggested some patients could benefit from a short period of bisphosphonate administration after hip replacement surgery. For example, patients at risk for osteoporosis could undergo DXA-scanning before surgery and if the baseline BMD is low then a short period of bisphosphonate administration could be justified. Similarly, if the operating surgeon identifies low quality bone intraoperatively, bisphosphonate treatment may be justified. Administration of alendronate for six months seems to be long enough to prevent early periprosthetic bone loss. However, the safety of this drug and cost-benefit of the treatment must be critically evaluated when using it generally for this indication.

6.6 BONE HISTOMORPHOMETRIC FINDINGS IN THE ILIAC CREST AND IN PROXIMAL FEMUR WITH PATIENTS SUFFERING FROM OSTEOARTHRITIS, IS THERE A CORRELATION?

OA is often considered a bone-forming disease. When the disease in the joint progresses, bony osteophytes enlarge, thus creating new bone. Histologically in the presence of OA the amount of osteoid is significantly increased and the cancellous bone thickness and volume are also increased. The more the cartilage is damaged the deeper changes can be seen in the subchondral bone. Usually sclerotic OA changes can be seen in the subchondral bone but in other areas even osteoporosis is possible.
It is not yet clear if changes in bone quality can be seen in areas not affected by OA. Gevers et al. showed that patients with hand OA have increased bone mass in the iliac crest compared to patients without OA. Fazzarali et al. showed that bone histomorphometric qualities from iliac crest did not differ between patients with or without OA. They concluded that iliac crest is a poor predictor of OA in general. (Fazzarali et al. 1992, Gevers et al. 1989)

We showed that the lower the bone trabecular volume in the proximal femur and in the iliac crest was, the more prominent was the BMD loss after THA. No significant correlation of other bone turnover measures with changes in BMD were found. Our study was small, but it suggests that periprosthetic BMD changes could not be predicted by bone biopsies. The bone loss around prosthesis is more likely due to the stress shielding phenomenon than due to general bone turnover.

### 6.7 FURTHER STUDIES

Our studies are limited because the small number of patients in each study. Further studies should be made with larger sample sizes in order to have a better statistical power.

The impact of THA on postoperative BMD loss is well documented also in the long follow-up period, but the association between periprosthetic bone loss and adverse clinical outcomes (aseptic loosening and periprosthetic fractures) remains unknown. Since rate of these complications remain relatively low even in the long term, these studies would require a large study population with DXA measurements and a long follow-up time.

Because hip resurfacing arthroplasty was previously quite popular there are a vast number of patients living with this type of implant. According to Finnish Arthroplasty register a total of 4895 HRAs were implanted during the years 2001-2014. Many of these patients have not undergone revision surgery despite the known problems associated with HRA. Probably a more physiological load transfer in the proximal femur had positive effect on implant survival if metal debris was avoided. Also, most of the HRA patients were relatively young males and the preoperative bone quality was better than in conventional THA patients, which could have an affect on the results. However, nowadays it is impossible to study how HRA would act in a more heterogenous population due to its known problems. It would be interesting to study if the femoral neck narrowing phenomenon becomes more frequent over time and to study what happens to the BMD in long term.

The effect of alendronate to the postoperative periprosthetic BMD is quite well documented, but the correlation between the restoration on BMD and its possible clinical advantages should be investigated in a large study population and with a long follow-up.

Clinical OA is a well-known disease, but the underlying causes to this disease are still unknown. It is possible that the role of bone metabolism in OA is more important than thought. Although we could not show that general bone remodeling is
associated with periprosthetic bone changes, more quantitative histological studies investigating the interaction between bone and cartilage are warranted. The causes of clinical OA are, of course, multifactorial, but as shown in previous studies OA may actually be a more generalized bone disease than thought. More studies are required to investigate the correlation between bone quality parameters in bones and sites not affected by OA to prove this hypothesis.
7 CONCLUSIONS

Based on the present study, the following conclusions can be drawn:

1. There is significant periprosthetic bone loss after total hip arthroplasty within one year after the surgery. When a good prosthesis-bone integration with or without cement is achieved, the rate of the periprosthetic bone loss decreases after the first post-operative year, and the bone loss reflects normal aging.

2. Hip resurfacing arthroplasty seems to preserve the bone stock of the proximal femur in a selected population. This may be related to more physiological load transfer along the proximal femur after HRA.

3. Alendronate seems to decrease early periprosthetic bone loss after arthroplasty. The positive effect may last up to five years postoperatively.

4. Low trabecular bone volume (BV/TV) both in the proximal femur and iliac crest associates with increased periprosthetic BMD loss after THA. We suggest that bone loss around the femoral stem is predominantly affected by local phenomena, like stress shielding or bone damage due to operation, and not by the patient’s general bone remodeling status.
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Hip arthroplastic surgery provides excellent results in terms of relieving pain and restoring motion. However, it affects proximal femoral biomechanics and causes changes to proximal femoral bone mineral density. The main purpose of this dissertation was to study these bone mineral density changes in proximal femur after total hip arthroplasty, hip resurfacing arthroplasty and if bisphosphonates could have an affect to the proximal femoral bone loss.