Summary

Osteoarthritis of the knee that does not respond to conservative treatment can be successfully treated by total knee arthroplasty (TKA). Several designs of total knee prosthesis (TKP) for primary osteoarthritis of the knee are available. These designs can be roughly categorized by the method of fixation to bone, cemented or cementless, and by the type of bearing, fixed or mobile. In this thesis, we focus on a cobalt-chromium-molybdenum alloy (CoCrMo) cementless mobile-bearing TKP with good clinical outcome and long term survival rate. Nonetheless, changes are made to the TKP design, surgical instruments, and surgical approach. These changes have not yet led to improvement of clinical outcome after TKA. Ceramic coating of a TKP articular surface might improve wear, friction, and lubrication of interacting surfaces. Ceramic coating of cementless TKP bone-implant surface might improve osseointegration. Improvement of TKP tribological aspects and osseointegration might improve clinical outcome after TKA.

The general goal of this thesis was to evaluate the effects of changes in coating of TKP articular and bone-implant surface, TKP design, and bone mineral density on the clinical outcome of TKA. The following aims were addressed:

- To investigate the additional value of titanium-nitride (TiN)-coating on osteoconduction of CoCrMo implant material, on the clinical outcome of cementless mobile-bearing TKA, and on biocompatibility and wear of orthopaedic implant material in preclinical studies and on survival rate of orthopaedic implants in clinical studies.
- To assess the clinical outcome of cementless mobile-bearing TKA when modifications are made to the dimensions of the femoral and tibial component, and the insert of the TKP as well as the correlation of a patient related outcome measure with pain and performance-based functioning after cementless mobile-bearing TKA.
- To study complications related to osteopetrotic bone after cementless mobile-bearing TKA, and to explore the role of osteocyte morphology in osteopetrotic bone, and other bone mineral densities encountered in cementless mobile-bearing TKA.

Since chromium and cobalt ions negatively affect the growth and metabolism of cultured osteoblasts while enhancing osteoclastogenic cytokine production, we hypothesized, in Chapter 2, that TiN-coated CoCrMo surface would enhance osteoblast proliferation and/or differentiation and reduce osteoclastogenic cytokine production compared with a CoCrMo-surface. Murine osteoblast-like MC3T3-E1 cells were cultured for 1, 2, 4, and 7 days on smooth and porous CoCrMo and TiN discs. After culture, cell proliferation and cell differentiation were assessed. The production of the cytokines II-1β, II-6, and TNF-α was quantified. Increased proliferation and similar differentiation was found on smooth and porous TiN compared with CoCrMo surfaces. Cellular II-6 production was higher on porous CoCrMo compared with porous TiN. II-1β production was detected in only a few cultures on these surfaces, but TNF-α was not detected. Our findings suggest improved osteoconduction of MC3T3-E1 cells on TiN compared with CoCrMo surfaces.
with CoCrMo. The role of osteoblast-produced osteoclastogenic cytokines in osteoconduction remains unclear.

Whether the preclinical advantages of TiN-coating of CoCrMo result in less postoperative synovitis and better clinical outcome of TiN-coated CoCrMo cementless mobile-bearing TKP compared with uncoated CoCrMo cementless mobile-bearing TKP was investigated in Chapter 3. In a randomized clinical trial with 5 year follow-up, there was no difference in postoperative pain, revision rate, range of motion, swelling and temperature of the knee between TiN-coated CoCrMo TKP and uncoated CoCrMo TKP. Although there was no clinical benefit of TiN-coated CoCrMo TKP, the results of TiN-coated CoCrMo TKP were not inferior to uncoated CoCrMo TKP.

In Chapter 4, we performed a review of the English medical literature to identify the effects of TiN-coating on orthopaedic implant material in preclinical studies and to explore the influence of these effects on the clinical outcome of TiN-coated orthopaedic implants. In preclinical studies on biocompatibility, half of the studies showed an increased proliferation of cells cultured on TiN-coated implant material compared with the control material. Differentiation of cells cultured on TiN-coated implant material was similar compared with the control implant material. Most preclinical studies on wear showed a reduction of ultra-high molecular weight polyethylene (UHMWPE) wear and increased scratch resistance on TiN-coated implant material compared with their controls. Clinical cohort studies of TiN-coated orthopaedic implants showed a high survival rate of 92% to 100% with a mean follow-up of 15-79 months, except for one study with a survival rate of 56% at 26 months follow-up. Preclinical wear studies and clinical case reports demonstrated increased wear, coating failure, fretting and third-body wear. This might be due to the various coating processes of titanium alloys. Therefore, the TiN-coating process should be optimized and standardized for titanium alloy articulating surfaces. There are no reports of clinical adverse effects of TiN-coating of CoCrMo TKP. Since TiN-coating of cementless mobile-bearing CoCrMo TKP might positively influence aseptic loosening through improved osseointegration and reduction of UHMWPE wear, further research is needed to assess long-term clinical results of TiN-coated CoCrMo TKP.

Over the last years, there has been a paradigm shift from disease centered care to patient centered care. To evaluate the outcome of cementless mobile-bearing TKA nowadays, patient related outcome measures (PROM) become more important. A self-report questionnaire, the Oxford Knee Score (OKS) and its subscores for pain (PCS) and function (FCS), was correlated to the Visual Analogue Scale score for pain (VAS), the Knee Society Score (KSS), and a performance-based measure, the DynaPort Knee Score (DKS) in Chapter 5. We hypothesized that a higher correlation exists between the OKS and pain than between OKS and performance-based functioning. We found that all scores improved after surgery. Of all scores, only the DKS was influenced by sex, age and preoperative body mass index. The mean postoperative OKS and OKS PCS showed a high correlation with the VAS. The mean postoperative OKS and OKS
PCS showed moderate correlation with the DKS. The mean postoperative KSS showed high correlations with the OKS, the OKS PCS and the OKS FCS. The internal consistency of the items of the OKS PCS increased during follow-up reaching a Cronbach’s $\alpha$ of 0.9 which indicates that items within a questionnaire become redundant. The items of the OKS PCS might be over represented, emphasizing on pain within the overall OKS. These findings suggest that the OKS is more related to pain than to performance-based functioning. This is important when the OKS as PROM is used to evaluate the quality of orthopaedic care of patients with TKA.

In Chapter 6, the introduction of a new version of a cementless mobile-bearing TKP, the Low Contact Stress (LCS) was evaluated. In a retrospective cohort study with 5 year follow-up, revision and re-operation rate, KSS, OKS, and range of motion of the old version of cementless mobile-bearing TKP, LCS Classic, was compared with the new version, LCS Complete. There was no difference in revision rate between the LCS Classic (3%) and the LCS Complete (5%). There was no difference in mean KSS and OKS between the LCS Classic and the LCS Complete. However, a higher percentage of patients with a LCS Complete scored in the lowest quartile of the subscore of the KSS, the KSS Knee. Moreover, more than 5 degrees flexion contracture was found only in patients with a LCS Complete. This suggests a clinical relevant difference of the LCS Complete with the LCS Classic, after introduction of the LCS Complete. It is unknown whether this is caused by the change in design and associated surgical technique and instruments. Further investigation in future studies with the introduction of new designs is needed, since introduction of a new design might lead to suboptimal clinical results.

In Chapter 7, bone of patients with different bone mineral density (BMD) resected during cementless mobile-bearing TKA was used to explore the possibility that osteocyte morphology might play a role in various bone pathologies with different BMD. In bones of different pathologies with different BMD, matrix strains due to external loading are different. These matrix strains are likely sensed by the osteocytes, the putative bone mechanosensors. The mechanosensitivity of osteocytes appears to be strongly influenced by their morphology. Confocal laser scanning microscopy and nano-CT were used to quantitatively determine 3D morphology and alignment of osteocytes and osteocyte lacunae in human proximal tibial bone with relatively low (osteopenic), medium (osteoarthritic), and high (osteopetrotic) BMD. Osteopenic osteocytes were relatively large and round, osteopetrotic osteocytes small and discoid shaped, and osteoarthritic osteocytes large and elongated. Osteopenic osteocyte lacunae showed 3.5 fold larger volume and 2.2 fold larger surface area than osteoarthritic lacunae, whereas osteopetrotic lacunae were 1.9 fold larger and showed 1.5 fold larger surface area than osteoarthritic lacunae. Osteopetrotic osteocyte lacunae had lower alignment than osteopenic and osteoarthritic lacunae as indicated by their lower degree of anisotropy. The differences in three dimensional morphology of osteocytes and their lacunae in long bones of different bone pathologies with different BMD might reflect an adaptation to matrix strain due to different external loading conditions. Moreover, since direct mechanosensing of matrix strain likely occurs by the cell bodies, the differences in osteocyte
Chapter 10

morphology and their lacunae might indicate differences in osteocyte mechanosensitivity. The exact relationship between osteocyte morphology and bone architecture is complex and deserves further study.

Autosomal dominant osteopetrosis (ADO) is a sclerosing bone disorder due to failure of osteoclasts to resorb bone. The increased chance for iatrogenic fractures due to sclerotic bone causes difficulties during arthroplasty in ADO. ADO is divided into two types based on radiological findings, fracture risk, gene mutation and osteoclast activity. It has been suggested to list ADO type I as a “high bone density disorder” instead of a type of osteopetrosis. The differences between ADO type I and type II suggest less brittle bone in patients with ADO type I, and thus a smaller chance of peroperative fractures during cementless arthroplasty compared with ADO type II. A clinical case on cementless mobile-bearing TKA in a young patient with ADO type I is presented in Chapter 8. Postoperative radiographs showed a fissured fracture distal to the cone of the tibial component which was deemed stable. After one year, the patient was free of pain and had a knee flexion of 110 degrees. One-year postoperative radiographs showed no signs of the earlier fissured fracture. During follow up, total hip arthroplasty was performed and known major problems related to total hip arthroplasty in ADO type II were experienced. Therefore, the differences between ADO type I and ADO type II may not be clinically relevant for an iatrogenic fracture during arthroplasty in patients with ADO.

Finally, in Chapter 9, the results and the limitations of the studies are discussed and put in a broader context in three sections; osteopetrosis, titanium-nitride coating and clinical outcome, in relation to cementless mobile-bearing TKA.