In this thesis, fundamental and clinical research was performed regarding different aspects of cementless mobile bearing total knee arthroplasty (TKA) for the treatment of patients with symptomatic osteoarthritis of the knee. Concerns on the biocompatibility of cobalt-chromium-molybdenum (CoCrMo) alloy were raised [2, 15, 51]. Therefore, titanium-nitride (TiN) coating of CoCrMo implant material was introduced [33, 52]. We found increased MC3T3-E1 osteoblast-like cell proliferation, but similar differentiation on porous and smooth TiN-coated implant material compared to CoCrMo implant material. This might lead to enhanced osteoconduction of osteoblast-like cells on TiN-coated implant material compared to CoCrMo. On the other hand, a clinical trial comparing TiN-coated mobile bearing TKA with CoCrMo mobile bearing TKA, did not show differences in postoperative synovitis, improvement of clinical outcome or revision rate [49]. Several methods are used to apply TiN-coating to titanium alloy articulating surfaces that require surface treatment. Some of these methods have raised serious concerns, since fretting and third body wear occur [20, 40]. The benefit of TiN-coating of CoCrMo implants remains unclear and long-term follow up of these implants should be conducted.

After introduction of a new version of an established mobile bearing TKA, the percentage of patients with a low subscore of the Knee Society Score, the Knee score [24], increased. Whether this increase in the number of patients with a low Knee score is caused by changes in the design of the total knee implant or by the associated new instruments and surgical technique is unknown. The Oxford Knee Score as a patient-related outcome measure showed a higher correlation with postoperative pain than with performance based functioning, which should be taken into account when the Oxford Knee Score is used to evaluate the quality of care.

We found that cementless mobile bearing TKA was feasible, while total hip arthroplasty was quite hazardous in a young patient with osteoarthritis due to autosomal dominant osteopetrosis (ADO) type I. In osteopetrotic bone, as well as in osteopenic and osteoarthritic bone, the osteocytes and their lacunae showed significant differences in their morphology, possibly reflecting differences in osteocyte mechanosensitivity. The exact relationship between osteocyte morphology and bone architecture, however, is complex and deserves further study. Here the results as described in this thesis are discussed.

Osteopetrosis and cementless mobile bearing TKA
Incidentally, orthopaedic surgeons are faced with the challenge of young patients with severe debilitating osteoarthritis of the knee due to increased bone mineral density, as is the case in type I and II ADO [45]. These patients might benefit from a cementless TKA, because of suggested increased longevity of cementless TKA over cemented TKA [36, 38].

The cellular processes leading to fixation of a cementless total knee prosthesis resemble the cellular processes occurring during fracture healing [13]. The distinct difference is that bone grows on the implant by the process of osteoconduction followed by osseointegration, while during fracture healing the bone grows to the other part of the fracture. The initiation of fracture
healing and osteoconduction are alike; both fracture healing and osteoconduction start with the
formation of a blood clot between the bony parts that need to heal [13]. In this blood clot, fibrin
allows migration of osteoblasts to the implant surface, where they start to secrete bone [13]. This
so-called “woven bone” is produced and will be remodeled later by the bone resorbing activity
of osteoclasts and bone formation activity of osteoblasts [8]. Active osteoclasts are necessary
for bone remodeling, and therefore cementless TKA should not be performed in patients with
osteoarthritic knees due to ADO type II, as this is characterized by deficient osteoclasts [22]. This
is supported by histological findings in a case of a femoral fracture in a patient with ADO type
II, that still showed woven bone one year after fracture [14]. In the case of a patient with ADO
type I (Chapter 8), in which osteoclasts are not deficient [21], we did not observe any problems in
healing of the tibial fissure that arose at the time of prosthesis implantation. Although cementless
fixation of total hip implants is feasible in ADO, the procedure itself is hazardous [18]. Bone in
ADO type I is hard and brittle and the intramedullary canal is small, making it difficult to put in
a press-fit hip implant without causing a fracture. Therefore, we advise to use cemented total hip
implants in patients with sclerosing bone disorders such as ADO type I. For TKA, both cemented
and cementless implants might be considered in ADO I. In ADO type II however, periprosthetic
fractures are unlikely to heal and therefore we would advise cemented TKA.

During the process of osseointegration, osteoblasts produce bone on the implant’s surface
[13]. Some osteoblasts become embedded in the bone and become osteocytes. These cells form a
lacuno-canalicular network in bone [10]. Osteocytes are the mechanosensors of bone, and regulate
osteoblast and osteoclast activity depending on the prevailing mechanical loading conditions
[10]. Since osteocytes play an important role in bone remodeling, it is highly likely that they play
an important role in the fixation of the cementless total knee prosthesis as well.

Resected bone obtained from three patients with different bone mineral density who had
cementless mobile bearing TKA, was used to study the morphology of the osteocytes and
their lacunae. Different morphology of osteocytes and their lacunae were found in bone with
different bone mineral density, indicating differences in osteocyte mechanosensitivity (Chapter
7). Human osteocytes were visualized using fluorescence and confocal laser scanning microscopy
(CLSM), whereas the osteocyte lacunae were visualized using nano-computer tomography (CT)
scanning [50]. Comparing the volume of the osteocyte lacunae measured by nano-CT to the
height, length and depth of the osteocytes measured by CLSM, we gather by estimation that
the osteocytes will not fit their lacunae. This is probably due to the use of fluorescence without
additional contrast, which likely results in oversizing the representing image of the osteocyte.
Also, it is likely that the images of the osteocyte lacunae are downsized due to adjustment of
the threshold to increase the contrast between the osteocyte lacunae and the surrounding bone.
Ideally, correlative microscopy is used, which combines the capabilities of typically separate, but
powerful microscopy platforms [11]. The combination of CLSM and nano-CT would increase the
understanding of the morphology of osteocytes in their lacunae within the lacuno-canalicular
network. At this moment, there are no examples of correlative microscopy using CLSM and nano-CT.

Titanium-nitride coating of cementless mobile bearing TKA

It is likely that osteoblasts directly contact the implant material in cementless TKA [1, 13]. For osteoconduction, amongst others the proliferation and differentiation of osteoblasts is important [1, 13]. Adhesion of osteoblasts to the implant surface depends on surface microtopography and surface chemistry [27, 31]. Cobalt and chromium particles and ions have a negative effect on cells [51]. TiN on the other hand is inert [48]. In an in vitro study (Chapter 2) murine osteoblast-like cells were cultured on smooth and porous TiN and CoCrMo, in which the porous surfaces resemble the bone-implant surface of cementless total knee prosthesis. Higher proliferation and similar differentiation of these osteoblast-like cells was found on TiN compared to CoCrMo surfaces. Proliferation of osteoblasts is important in the progress of osteoconduction, but the process of osteoconduction is far more complex [1, 13].

The role of osteoblast-produced osteoclastogenic cytokines was examined. Cytokines IL-1β and TNF-α were measured in culture medium, but only IL-1β was detected in medium of a few osteoblast cultures. MC3T3-E1 osteoblasts are capable of production of these cytokines [4, 16, 19, 25, 39], but neither CoCrMo nor TiN surfaces triggered the osteoblasts to secretion of osteoclastogenic cytokines. IL-6 was secreted, but the role of IL-6 is debatable and dependent on the maturity of osteoblasts [5]. The role of osteoblast-produced osteoclastogenic cytokines in osteoconduction remains unclear.

The Low Contact Stress mobile bearing TKA system (LCS®, DePuy, Warsaw, IN, USA), has good clinical results [23] and a good clinical long term rating according to the Orthopaedic Data Evaluation Panel (ODEP, www.odep.org.uk). This system might be improved by using TiN-coating of the bone-implant surface and the articulating surface leading to better osseointegration and less polyethylene wear resulting in higher longevity of the implant. The LCS with a TiN-coating is only produced on request by the orthopaedic surgeon. It is therefore not easily available in higher numbers, as required for a randomized clinical trial. We used the CCI® (currently available as ACS® Basic, Implantcast GmbH, Buxtehude, Germany), a mobile bearing total knee system comparable to the LCS knee system, which is only available with a TiN-coating, to investigate the influence of TiN-coating on the postoperative outcome of TKA.

The CCI knee system was introduced in 2002, and might therefore be considered as a relatively new knee system. Currently, new knee systems are tested for implant migration as early as 2 years after surgery using radiostereometric analysis (RSA), because most tibial components migrate in the first year after implantation [41]. This seems an acceptable time period for manufacturers and orthopaedic surgeons to allow comparison of the behavior of the new prosthesis compared to the prosthesis already available on the market. RSA has been made available by Selvik et al. in 1978 [42], and thereafter clinical studies using RSA on knee implants followed quickly [3,
41]. A reduction of 22-35% of revisions for RSA-tested knee systems compared with non-RSA-tested knee systems have been observed [37]. The first digital RSA system dates from 1997 [26]. Increased accuracy in digital RSA with the use of tantalum markers was found in 2002 [26].

With RSA still evolving at the start of our clinical trial using the TiN-coated mobile bearing TKA in 2005, RSA was not implemented in the trial presented in this thesis. Currently, a study is conducted using RSA to measure migration of TiN-coated knee implants.

TiN-coating of implants, introduced to enhance scratch resistance and to lower the coefficient of friction of the implant’s articulating surface, is also advocated to protect the body against the potential harmful effects of Co and Cr ions, by sealing of the CoCrMo alloy [9]. This is especially important in the case of metal-on-metal prosthesis as used in total hip arthroplasty. In TKA, the implants articulation is metal-on-ultra-high molecular weight polyethylene (UHMWPE) where the release of metal ions from the implant is not a concern [32]. The release of metal ions from orthopaedic implants might cause metal hypersensitivity, or a problem in patients already hypersensitive to certain metals used in orthopaedic implants [34]. A comparison between uncoated CoCrMo TKA with multilayer coated (chromium-nitride, chromium-carbonitride, zirconium-nitride) TKA, revealed that sensitization for metal ions is rare and serum metal ion levels are not elevated in either uncoated CoCrMo TKA or multilayer coated TKA [32]. It is likely that TiN-coating of CoCrMo TKA shows the same incidence of sensitization to metal ions and similar serum metal ion levels compared to uncoated CoCrMo.

In our 5-year follow up study comparing TiN-coated CoCrMo TKA with uncoated CoCrMo TKA (Chapter 3), the focus was on the clinical results such as pain, range of motion, swelling and temperature. These clinical symptoms raise concerns for both the patient and the orthopaedic surgeon [30]. Since TiN is inert it was hypothesized that TiN-coated TKA causes less pain, swelling and/or increase in temperature of the knee, resulting in faster rehabilitation after TKA. Standard AP and lateral x-rays of the knee were made directly postoperative and at 1 and 5 year follow-up, but the variety of these x-rays were too high to perform proper follow-up. RSA would have been helpful as discussed earlier. Moreover, pre- and postoperative radiographic alignment was not assessed as a possible confounder for the postoperative outcome.

There was no difference in revision rate of TiN-coated cementless mobile bearing TKA compared to uncoated cementless mobile bearing TKA [49]. When TiN-coating of cementless mobile bearing TKA does influence osseointegration and wear of the implant a lower revision rate might be shown with long-term follow-up or a larger cohort of patients.

To assess the clinical benefit of TiN-coating of orthopaedic implants properly, a meta-analysis of available randomized clinical trials is needed. However, the quality of studies available in English medical literature is insufficient to perform such a meta-analysis. The presented literature review (Chapter 4) shows the advantages and disadvantages of TiN-coating of orthopaedic implants. It seems that in preclinical studies, a TiN-coating of implant material has advantages compared with uncoated implant material, while in clinical studies the advantage of TiN-coating
of implants is unclear. Another problem is the variation in processes to apply TiN-coating to either titanium alloys or CoCrMo. Often it is not reported to what degree of surface roughness the TiN-coating is polished. This might influence wear rate of UHMWPE and in case of metal-on-metal implants third body wear and failure of the coating.

The available case reports on retrieval of TiN-coated Ti6Al4V femoral heads on UHMWPE either post-mortem or after revision indicating breakthrough and fretting of the TiN-layer, are difficult to interpret [20, 40]. These cases are worrisome, but they would be more valuable when presented as part of a cohort study to create perspective. There are many variables in the articulation of an artificial joint that might be a cause for breakthrough or fretting of the TiN-layer. However, there are no adverse effects of TiN-coated TKA in our clinical trial or in another study [35] which could be related to the TiN-coating during follow-up.

Clinical outcome of cementless mobile bearing TKA
TiN-coating of cementless mobile bearing TKA showed similar results on postoperative synovitis, improvement on clinical outcome and revision rate compared with the standard CoCrMo cementless mobile bearing TKA [49]. Changes to total knee systems, prosthesis and instruments for implantation, are made for several reasons; sometimes new philosophies due to progressing insights lead to development of new systems, sometimes knee systems are changed due to feedback of orthopaedic surgeons experiencing problems with either the implant during surgery or during follow up, or with the instruments for implantation. These changes to new systems should bear in mind reasonable improvement of the results after TKA, otherwise there is no good reason to change the knee system at all. Sometimes changes are made to knee systems from a commercially point of view. The larger orthopedic device makers are billion dollar companies, making profit of the orthopaedic implants, trying to stay ahead of the competition using innovations.

Ideally, one would conduct a randomized clinical trial to compare the results of a new version knee system with the old version. However, when the old version knee system is no longer available, and a change to a new version is needed, then the results can only be evaluated using a retrospective cohort study. With the introduction of a new version knee system the orthopedic surgeon experiences a learning curve, with likely a higher incidence of suboptimal results (Chapter 6), or even failures compared to the old version knee system. When there is no clear problem with an old version knee system, the introduction of a new version knee system should be scrutinized, as the patient pays the price with suboptimal results which might lead to revision surgery.

Currently, the reasons for revision for TKA are loosening, infection, instability, periprosthetic fracture and arthrofibrosis [44]. For early revisions with a mean of 0.84 years after primary surgery (range, 1 day-1.97 years,) the main reasons for revisions in order of highest prevalence were infection, loosening, instability, arthrofibrosis and periprosthetic fracture [44]. For late revisions with a mean of 6.9 years after primary surgery (range, 2.01-30.36 years), the main reasons for revisions in order of highest prevalence are loosening, infection and instability [44]. Compared
with the results on reasons for early revisions ten years ago [43], there is a higher percentage
of infection and periprosthetic fractures nowadays, but a lower percentage of instability,
arthrofibrosis, PE wear, malalignment/malposition or extensor mechanism deficiency [43, 44]. A
higher percentage of loosening and infection, but a lower percentage of instability, arthrofibrosis,
PE wear and malalignment/malposition concerning reasons for late revisions compared with
ten years ago was found nowadays [43, 44]. The development of more resilient biomaterials
remarkably decreased PE wear as a reason for revision [44]. With the increase of incidence of
primary TKA, it is still estimated that there will be a related increase of revisions after primary
TKA [28, 29]. Sadly, after revision TKA patients have lower scores on patient related outcome
measures compared with primary TKA [17].

Pain, caused by osteoarthritis of the knee, is a key parameter when the indication for TKA
is set. The severity of this pain is not easily objectified [6]. Moreover, a patients’ coping process
with pain, such as helplessness, magnification and rumination, might exaggerate the value of
the painful knee [46]. It is also one of the factors that leads to persisting pain after TKA [6].
Depression and anxiety influence pain as well, leading to increased pain one year after TKA [7].
Catastrophizing, anxiety and depression were not scored in the studies presented in this thesis.
For the clinical study conducted (Chapter 3), an effort was made to screen patients for major
depression using a tool developed for general practitioners [47]. However, this questionnaire was
too dichotomous in its use to implement in our clinical study. In future studies, confounders such
as catastrophizing, anxiety and depression should be scored and it should be taken into account
when preoperatively assessing a patient for TKA.

In the studies in this thesis pain was only scored as a visual analogue scale score for continuous
pain, but not specified per activity. We found only weak to moderate correlation of the visual
analogue scale score for pain with the performance-based function measure, the DynaPort Knee
Score. It would have been interesting when the activity-specified pain score could be correlated
to the DynaPort Knee Score, to see whether performance-based function is influenced by pain.

In our study, the Oxford Knee Score and the subscales for pain and function, the Knee
Society Score and the DynaPort Knee Score, improve after surgery (Chapter 5). The correlation
coefficient of these scores would be 1, when lines of improvement are parallel. The very moderate
correlation coefficient of the Oxford Knee Score Pain Component with the DynaPort Knee Score,
suggests that the Oxford Knee Score Pain Component increases faster after surgery then the
DynaPort Knee Score. This indicates that pain decreases faster after surgery than performance
based function improves. This is important information when informing the patient during
preoperative consultation, as fine-tuning the patient’s expectations is an important step to achieve
a satisfied postoperative patient.

“Change is certain, progress is not”. This quote [12] reaches the essence of this thesis. Changes
are made to designs of total knee prosthesis, bearing improvement of the results of TKA in mind.
Currently, several designs of total knee prosthesis used in TKA have a high survival rate and
good clinical outcome, which leaves little room for improvement. It is likely that changes in
the prosthesis' design are insignificant to the clinical results of TKA. Moreover, changes might
backfire and result in lower survival rates and inferior clinical results. Another way to improve
postoperative outcome, which might lie in the preoperative assessment of a patient with knee
pain, is to optimize a patients’ expectations and to try to identify the patients who tend to
catastrophize and are anxious and depressed.
References