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SUMMARY

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Total hip arthroplasty (THA) is an effective and successful procedure for the treatment of osteoarthritis, fractures, avascular necrosis, and tumors of the hip joint. Because of its success there is an increasing broadening of the indications for THA, and the implantation of THAs are becoming more widespread. Unfortunately prosthesis survival is limited due to (a)septic loosening or failure of the implant, and revision surgery may become necessary. The loosening process and the removal of failed THAs frequently results in bone defects. Impaction bone grafting is a well established method dealing with bone defects during orthopaedic revision procedures. Allograft and/or autograft bone is used to restore bone defects, and after the operation procedure a remodeling process incorporates the graft bone into the host bone. In this manner the initial bone stock is restored. This method provides a biological solution to address the loss of bone, and will facilitate future revision procedures.
In this thesis, clinical, biomechanical, and biological aspects of impaction bone grafting are enlightened.

Chapter 1 provides a general introduction with an overview of the history and background of THA, revision hip surgery, and impaction bone grafting. The reasons for revision surgery and the different possibilities in revision surgery are described. Also the surgical technique of impaction grafting, and the post-operative remodeling and incorporation process is explained. New developments in impaction grafting are described, such as the use of biomaterials and mesechymal stem cells to reduce the amount of allograft bone needed and to improve the incorporation process. The research questions addressed in this thesis have been formulated in light of the background information provided in this chapter.

In **chapter 2** a clinical follow up study of an uncemented screw cup for primary total hip arthroplasty is presented. Radiographs of 72 uncemented acetabular implants with a mean follow-up of 6.5 years were analyzed to measure the wear of the insert. High insert wear rates of 0.13 mm/year were found due to an inferior quality polyethylene. Large osteolytic cyst formation was observed resulting from “back wear” caused by the screw holes in the metal shell of the cup. High revision rates are expected, and loss of bone stock is a major problem encountered. This study illustrates the potential indication for the use of bone impaction grafting to restore bone defects.

Impaction bone grafting can be of value in revision procedures as shown by the encouraging clinical and radiological results of impaction grafting revision knee surgery, which is described in **chapter 3**. In this study primary cemented knee

implants in combination with impaction bone grafting were used to restore bone defects in revision knee surgery. Good clinical and radiological results were obtained.

Chapter 4 shows that the clinical results of impaction bone grafting are not always optimal. In the clinical follow up study presented, with a mean follow-up of 7.2 years (range: 1.6 to 9.7 years), 20 of 71 acetabular impaction grafting revision procedures needed re-revision for aseptic loosening, giving an overall survival of 72% (95% CI, range: 54.4 to 80.5%). In this study we attempted to identify key factors for good long-term implant survival. All patients were assessed according to the American Academy of Orthopedic Surgeons (AAOS) classification for bone loss, the amount of bone graft required, thickness of the graft layer, signs of graft incorporation, and use of augmentation meshes to reconstruct the bone contour.

Fourteen (70%) of the failures had an AAOS type III or IV bone defect. In the failed group, poor radiological and histological graft incorporation was seen.
The results of this study suggest that impaction allografting in acetabular revision with severe bone defects may result in a less favorable outcome than has been reported previously.

The application of new materials could be of value to improve clinical outcome and to overcome specific shortcomings of the impaction grafting technique. A realistic human model is necessary in order to mechanically and surgically test these new materials. For this purpose, human cadaver bones that have been embalmed in a formaldehyde solution are frequently used. The long-term effect of embalming or freezing on the mechanical properties of bone is however unknown. As human cadavers are generally stored for longer periods of time before use, we investigated the long-term effect of embalming or freezing on the mechanical properties of cortical bone in **chapter 5**.
After 5 different storage periods (0 to 12 months) the effect of embalming and freezing on torsion and bending stiffness and strength was evaluated. The effect on hardness and bone mineral density was also assessed. After one year no statistically significant effect in non of the studied parameters was observed when comparing embalmed or frozen bones to a fresh reference group. We concluded that embalmed or frozen bones can thus safely be used of mechanical testing and surgical handling studies.
This study validated the model used to test the application of new materials in impaction bone grafting as described in chapter 6 en 7.

Metal support meshes are used as a mould for the graft in case of segmental bone defects during impaction grafting revision procedures. Metal meshes function well, but there are potential disadvantages associated with their use,

such as the eclipse of the remodeling process as observed on radiographs, stress shielding, and the need for removal of an additional foreign body when implant infection develops or when re-revision is needed. Stainless steel meshes also negatively influence the remodeling process. Most of these disadvantages can be avoided using bioresorbable meshes. In **chapter 6** a surgical simulation model is used to investigate the surgical and mechanical suitability of a terpolymer (poly L-lactic acid, poly D-lactic acid and polyglycolic acid) bioresorbable molding mesh for use in impaction grafting revision surgery. The meshes were used to restore a 5x5 cm calcar defect. The mechanical deformation of the meshes was measured during the surgical procedure and post-operatively by cyclic loading with strain gauges, and the surgical feasibility was also assessed.
After heating the meshes to 70°C, all meshes were surgically suitable. The exterior surface deformation of the meshes during the surgical procedure and postoperative mechanical loading did not exceed 4500 μm/m. The meshes were not damaged in a four-point bending test although deformations higher than 19,000 μm/m were reached. Therefore the results of this study suggest that this terpolymer bioresorbable mesh seems to have sufficient initial mechanical properties to warrant additional preclinical in vivo study.

The golden standard in impaction grafting revision surgery is the use of allograft donor bone to restore bone defects. There are however concerns about pathogen transmission, the shortage of supply of donor bone, and the high costs. Bone graft extenders such as tricalcium phosphate (TCP) and hydroxyapatite (HA) have been developed to reduce the need of donor bone. TCP and HA have proven biocompatibility and the ability to act as an osteoconductive material. These materials are best combined with donor bone in a weight relation of 50:50 thus reducing the required amount of donor bone by half.
In **chapter 7** we evaluated the surgical and mechanical feasibility of a TCP/HA graft extender for the use in femoral impaction grafting revision procedures in a human cadaver model. The surgical applicability was assessed during a simulated revision procedure. During this procedure, force readings were performed with a specially designed impaction hammer. Post-operatively a mechanical loading program was applied to test the mechanical stability of the construct.
The addition of TCP/HA to allograft increased the risk of producing a fissure in the femur during the impaction procedure, but provided a higher initial mechanical stability during post-operative loading. This difference may be attributed to the lower compressibility and the near absence of visco-elastic behavior of the TCP/HA mixed with bone. From a biomechanical point of view, we conclude that the investigated TCP/HA is a viable graft extender for use in

impaction grafting of the femur. In light of the current shortage of donor bone, graft extenders may have an important role in impaction grafting. It is however very important that surgeons are aware that TCP/HA mixtures need to be handled differently than 100% allograft.

As stated above, a major clinical problem in impaction bone grafting is limited donor bone availability and pathogen transmission. Therefore there is an ongoing search for alternative graft materials and methods to improve bone remodeling. An alternative way to reduce the amount of allograft bone needed, is to search for biological solutions. With the use of growth factors the patient's bone cells (osteoblasts) could be stimulated to produce more matrix, thereby increasing the speed of the remodeling process. Alternatively, the widely available cell sources like autologous adult mesenchymal stem cells (MSC's), could be transplanted to the graft site in combination the growth factors and a scaffold thereby reducing the need for allograft bone. Adipose tissue-derived mesenchymal stem cells (AT-MSCs) are easily accessible, have a large biological availability, and have minimal donor site morbidity. The use of AT-MSCs might be attractive to increase remodeling, similar to osteoblasts and/or vital cells from bone-bank bone. In addition, growth factor application might stimulate AT-MSC proliferation and/or differentiation, also resulting in increased bone remodeling. In **chapter 8** we investigated the effect of bone morphogenetic protein-7 (BMP-7) on expression of osteogenic factors by AT-MSCs, osteoblasts, and vital cells from bone-bank bone.

BMP-7 increased gene expression of osteopontin (by 8.4-fold), but not collagen-1, alkaline phosphatase, or runx-2 in AT-MSCs at 1 week. It decreased alkaline phosphatase activity at 3 weeks, but not 1-2 weeks. BMP-7 did not affect runx-2 expression in osteoblasts, but it down-regulated the number of osteoblasts and vital bone-bank cells.

These results suggest that the anabolic effect of BMP-7 in bone grafting can be explained by stimulated precursor cell differentiation. Transplantation of large amounts of autologous osteogenic precursor cells in the presence of BMP-7 might enhance remodeling with reparative implications for bone tissue.

Chapter 9 contains a general discussion, and answers to research questions are given.