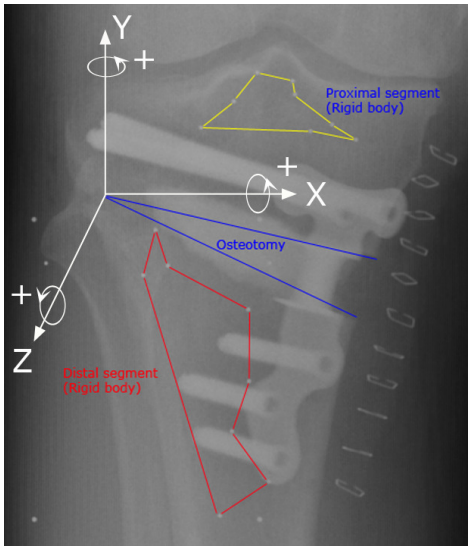
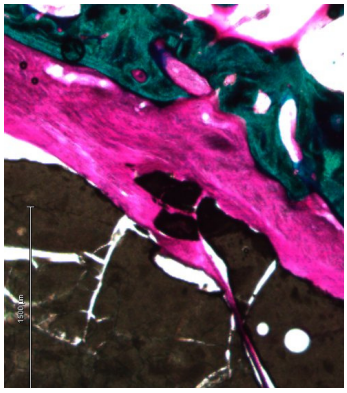
HIGH TIBIAL OPEN-WEDGE OSTEOTOMY
THE INFLUENCE OF DIFFERENT BONE GRAFT MATERIALS ON BONY HEALING
BIOMECHANICAL AND BIOLOGICAL CONSIDERATIONS

PhD thesis

Thomas Lind-Hansen





Faculty of Health Sciences
University of Aarhus
Denmark
2009

From
Northern Orthopaedic Division
North Denmark Region
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Facts are meaningless. You could use facts to prove anything that's even remotely true!

Homer Simpson

List of papers

This thesis is based on the following papers:

I. Calcium phosphate cement enhances primary stability of open-wedge high tibial osteotomies. Two biomechanical studies in cadaveric and composite tibias.
Thomas Lind-Hansen, Poul Torben Nielsen, Juozas Petruskevicius, Benny Endelt, Karl Brian Nielsen, Ivan Hvid, Martin Lind.
Submitted

II. Open-wedge High Tibial Osteotomy. A randomized study of three different bone grafting materials with two years follow-up. Roentgenstereometric analysis and clinical outcome.
Thomas Lind-Hansen, Martin Lind, Poul Torben Nielsen.
Manuscript

III. Open-wedge osteotomy. Histomorphometric evaluation of three bone graft materials. A randomized controlled study.
Thomas Lind-Hansen, Martin Lind, Poul Torben Nielsen.
Manuscript

The papers will be referred in the text by their Roman numerals (I-III).

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Preface

This PhD thesis is based on scientific work conducted during my enrolment as PhD student at the faculty of Health Sciences, Aarhus University, from 2005-2009. In the period I was employed as research assistant at the Orthopaedic Division, North Denmark Region, Aalborg Hospital - Aarhus University Hospital.
The clinical study was conducted at Department of Orthopaedics, Farsø Hospital, Orthopaedic Division, North Denmark Region. The biomechanical study was conducted at the Department of Production (IProd), Aalborg University. Preparation and evaluation of biopsies were done at The Orthopaedic Research Laboratory, Aarhus University Hospital.
I am grateful to my co-authors and especially my two principal supervisors: My main supervisor Martin Lind for always keeping us on track with his overview and constructive criticism, and never failing speedy feedback, and Poul Torben Nielsen for his support, catching and indefatigable enthusiasm, and friendship.
At the Orthopaedic and Radiological Departments at Farsø Hospital, I thank the staff for supportive interest and encouragement. Especially, I thank my surrogate mothers, Gitte Broholm and Ulla Hornum, whose enthusiastic work and planning smoothened the project.
I thank the people at IProd, for guiding and tolerance, when cadaver bones were introduced to their laboratory, and the skilled and kind laboratory technicians, and people at The Orthopaedic Research Laboratory, for introducing me to, and helping me with the histomorphometric evaluation.
I thank all my colleagues and friends at the Orthopaedic Division for good humour, advice and support. I owe particular thanks to Ole Simonsen and Mogens Berg Laursen for help, encouragement, support and friendship, chief consultant Hans Peter Jensen for patience and flexibility, and secretary Mette Ramsgaard for helping with the fundraising..
I would like to thank my friends and fellow PhD students Ramune Aleksyniene, Ren Gang and Juozas Petruskevicius for their support and sharing the joys and worries of orthopaedic research.
Finally, I thank my lovely family: My patient wife Anne for taking care of me and our lovely children, Sofie and Marius. You remind me of what really matters.

Acknowledgements - Disclosures

Thanks to “The Program of Body Donation to Medical Science, Institute of Anatomy, Aarhus University”, without which the biomechanical study would not have been possible.

The study was financially supported by the following non-commercial institutions:
- Vestdansk Sundhedsvidenskabeligt Forskningsforum
- The Danish Rheumatism Association
- The Opel Family Foundation
- The Spar Nord Foundation
- Aarhus Universitets Forskningsfond
- North Jutland Medical Association Research Foundation

During the course of the PhD study I have benefited from institutional research support from the following company with commercial interests in this research area:
- Biomet Denmark

Contents

Summary

Knee axis corrective open-wedge high tibial osteotomy is a well established treatment of unicompartmental knee osteoarthritis in the young and active patients.
The studies in the present thesis focus on the healing of the bone gap that is created with the open-wedge technique.
Currently, limited weight bearing is usually prescribed in the first postoperative weeks (usually six weeks), regardless of implant and bone grafting material. Recently, osteotomy stability has improved with new implant design, and the short term outcome seems to have improved. But it is still unknown if different bone grafting materials provides further benefits regarding osteotomy stability, healing and clinical outcome of the procedure.
The aim of the studies in this PhD thesis therefore was to examine the influence on stability, healing and clinical outcome, of different bone grafting materials as supplement to internal fixation in the open-wedge osteotomy technique.
Specifically we investigated the effect of injectable calcium phosphate cement (ICPC) compared to no graft, in a biomechanical study, since ICPC offers high initial compressive strength and osteoconduction, and in a randomized clinical study we compared ICPC with two types of bone autograft: Local bone autograft and iliac crest bone autograft.
We conducted two studies: a biomechanical study, and a randomized controlled study.
Biomechanical study: The study investigated the, in vitro, primary stability of the open-wedge construct with and without ICPC as supplement to internal fixation. The study showed that ICPC improved the stiffness and stability of the construct, and protected the construct from increasing damage during cyclic loading, and increased the load-to failure significantly. It was also found that the construct even without reinforcement of ICPC seemed strong enough to withstand the approximated loads found during walking.
Randomized controlled study: In the study 45 patients were randomized to the three different bone grafting materials: ICPC, local bone autograft and iliac crest bone autograft. The patients were followed for two years with investigation of stability, measured with roentgenstereometric analysis (RSA), clinical outcome measured with the knee injury and osteoarthritis outcome score (KOOS), and graft healing evaluated after one year by histomorphometric analysis.
RSA showed that only minor migration of the proximal tibia took place after osteotomy in the study period regardless of bone grafting material. All three groups migrated the most during the first three months, after which migration declined.
The ICPC group had less improvement in all clinical subscores (Knee and Osteoarthritis Outcome Score) at almost all time points, though no statistically significant differences were found, apart from the quality of life assessment after two years, where statistically significant differences were found between local graft and ICPC.
Histomorphometric analysis revealed that the two bone autograft groups healed to the same quality based on bone volume fractions and trabecular thickness. On the other hand ICPC remodeled slowly and induced a mixed soft tissue response with both bone and soft tissue ongrowth which might delay the remodelling process.
In conclusion we found that ICPC stabilized the construct in vitro and to some extent in vivo. Clinically ICPC seemed to perform less well than the other groups especially at the end of the follow-up period. A reason for this could be that ICPC only remodels slowly and induces a varying soft tissue response which perhaps also is the reason why the ICPC group doesn't perform better regarding migration. The findings warn of the use of ICPC as a bone grafting material in open-wedge HTO and verify that local autograft is safe to use in moderate sized osteotomies.

Introduction

Osteoarthritis (OA) of the knee is a potentially disabling disease, and the treatment of the young and active patient with early stages of unicompartmental osteoarthritis still remains a challenge. Corrective osteotomy of the knee in the treatment of painful unicompartmental osteoarthritis was first described by Jackson in 1958(1). HTO unloads the arthritic knee compartment and shifts the mechanical axis to the healthy compartment, thereby reducing pain and slowing the degenerative process (2-7). Today the surgical options include total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), and high tibial osteotomy (HTO) (8;9).

In recent years, open-wedge HTO has been preferred over the closed wedge technique (10;11). The methods used are either distraction by hemicallotasis with external fixation, or acute opening and internal fixation (5;12-14). The latter, however, leaves a gap with a medial opening often exceeding 1cm. To secure bony healing of the osteotomy, different bone graft materials are suggested by various authors. Autograft is considered the gold standard as it secures healing (5;12;15-17) but also includes disadvantages, i.e. limited availability and donor-site morbidity (18). Another alternative is allograft which entails a minor risk of virus transfer (19). Several bone substitutes have been introduced for gap healing in open-wedge HTO, either alone or in combination with autograft or allograft (12;16;17;20-22). With or without grafting, delayed healing is reported in up to 10 % of operations performed, and is associated with implant failure and loss of correction resulting in inferior results (fig 1). (5;12;15-17;20-23). With optimal internal fixation, bone grafting material and postoperative rehabilitation regimens these problems could be avoided. Injectable calcium phosphate cement (ICPC) could be beneficial as bone substitute, as it offers osteoconduction and initial high compressive strength (24-27) and, in theory, enhances the primary stability, potentially allowing immediate full weight bearing, without compromising the osseous consolidation.

The present thesis focuses on the influence of bone grafting materials, on osteotomy healing.

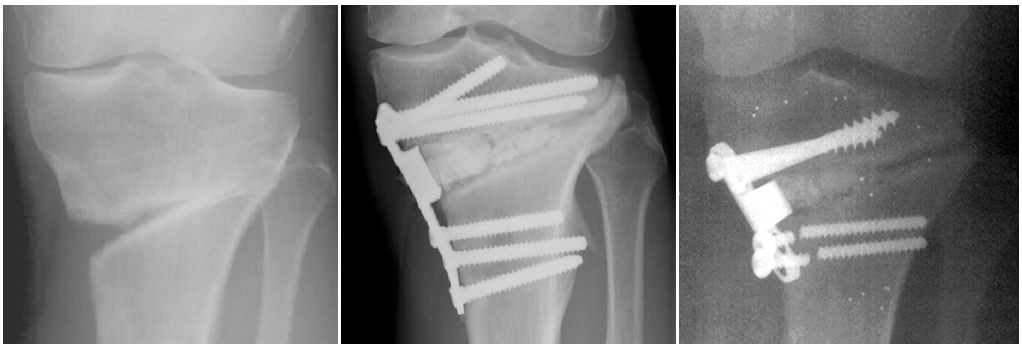


Fig. 1
Left: Incomplete gap filling
Middle: Delayed healing
Right: Delayed healing with implant failure

Aim of the PhD study

The overall aim of the studies included in this PhD thesis was to investigate the possible benefits of different bone grafting materials used in open-wedge HTO as supplement to internal fixation: injectable calcium phosphate cement (ICPC), local bone autograft, and iliac crest bone autograft.
Specifically we wished to test the influence of bone grafting materials on stability, and their ability to maintain the desired correction, the biologic reaction, and clinical outcome.
Therefore, a biomechanical study (study I) was set up to test the primary stability of the open-wedge construct (with and without ICPC) in terms of axial cyclic loading mimicking normal gait, and axial load-to-failure.
In a randomized, clinical trial we tested the eventual mechanical and clinical effects (study II), and the biological effects (study III), of the three grafting materials, over a 2 year period.

Hypotheses

Study I:
ICPC enhances primary stability of the open-wedge construct and thereby:

1. Minimizes displacement after cyclic loading mimicking normal gait
2. Increases load-to-failure

Study II:
ICPC improves primary stability leading to:

3. Improved stability after one year measured with RSA
4. Improved clinical outcome after one year

Study III:
ICPC is osteoconductive and biocompatible leading to:

5. Resorbtion and bone remodeling as estimated with histomorphometric analysis after one year

Grafting with iliac crest bone autograft and local bone autograft promotes osseous healing leading to:

6. Bone volume and trabecular thickness comparable to normal bone

Background

Osteoarthritis (OA) of the knee is a potentially disabling disease and the treatment of the young and active patient with early stages of unicompartmental osteoarthritis still remains a challenge, and with an expected increasing prevalence of knee osteoarthritis, optimal treatment regimens are needed for all stages of knee osteoarthritis (28;29).

Promising results of corrective osteotomy of the knee in the treatment of painful unicompartmental osteoarthritis with a "lateral deformity" was first described by Jackson in 1958 at the Sheffield Regional Orthopaedic Club (1). Later they confirmed their findings (30;31) together with Wardle, Venemans, Torgersen and Coventry (2;32-34), and argued that arthroplasty was "not yet reliable and is only rarely indicated in osteoarthritis"(35).

After the initial success, osteotomy was somewhat considered a demanding procedure, with frequent complications and unpredictable outcome. At the same time knee arthroplasty was increasingly successful, almost entirely replacing osteotomy (11).

A few studies have compared UKA with HTO, all studies on older populations (>60 years):

Ivarsson and Gillquist, and Börjesson et al. found that patients treated with UKA achieved better function after respectively six and tree months, including increased maximal walking speed (36;37).

Stuckenbort-Colsman et al. compared unicompartmental knee replacement with closed wedge HTO in a randomized study. They found that HTO resulted in better knee-, and function-scores using the Knee Society Scores, but also found more intra- and postoperative complications in the HTO group, and that survival was inferior for HTO than UKR. They conclude that UKR is a better alternative in the treatment of unicompartmental osteoarthritis in patients older than 60 years. Their study population were older (67 years) than the usual HTO candidate, and it could also be noted that the obtained correction perhaps were insufficient (0.25° varus), contributing to the higher revision rate for HTO (38).

However, younger patients treated with knee arthroplasty, and particularly unicompartmental knee arthroplasty, still have increased risk for revision (39;40).

A re-appreciation of osteotomies followed when osteotomies were considered an important supplement to ligament reconstruction. So, with better guidelines, osteotomy is still a valuable treatment in appropriately selected patients with unicompartmental knee disease, including young active patients with unicompartmental osteoarthritis, and correction of eventual malalignment when performing ligamentous reconstruction and chondral procedures (9;41-43).

Rationale of HTO

The purpose of the operation is to relieve pain by unloading the arthritic joint compartment by changing the mechanical axis, but it is not known why osteotomy relieves the pain. When Jackson described his results in 1963, there were different opinions on the subject. Some suggested that it could be contributed to division of nerves found in the cancellous bone, some suggested a mechanical element, Jackson himself meant that the pain was a result of stretched ligaments and excess pressure on cartilage (31).

Agneskirchner et al. found, in a biomechanical cadaver study, that shifting of the mechanical axis from medial to lateral resulted in decreased intra-articular pressure in the medial compartment and corresponding increased pressure in the lateral compartment. As soon as the mechanical axis were shifted to neutral position higher pressure where recorded laterally than medially. In the second part of the study they found that an osteotomy with a alignment of 62% valgus, resulted in increased cartilage pressure, probably because of tightening of MCL following the osteotomy, and only a complete release of MCL decompressed the medial compartment (44).

Several studies have investigated if the clinical improvement after HTO could be attributed to the correction achieved and eventual cartilage regeneration. Tjörnstrand et al. found that precise correction prevented further progression of the disease without further radiographic narrowing of cartilage, and in some instances with radiographic improvement of the cartilage (7;45). At arthroscopy two years after HTO, Odenbring (46) found fibrocartilaginous regeneration if a valgus overcorrection had been achieved. However no correlation could be found between cartilage regeneration and clinical results. After osteotomies, where more than 5° of valgus where achieved, Koshino et al. (47) found significant improvement of the cartilage at open arthrotomi of 146 knees after 24 months. Further he found that improvement of the cartilage with mature regeneration where found more frequent in patients with opening of the medial knee compartment, as compared to those with unchanged with of the compartment, on standing x-ray. Clinically better scores were associated with cartilage regeneration. At arthroscopy 18 month postoperatively Kanamiya (48) found that clinical scores improved significantly after osteotomy, in patients where full cartilage regeneration was found, as compared with patients where no regeneration was found. A mechanical axis passing the lateral knee compartment resulted in improved clinical results.

Today many surgeons use the recommendations and principles outlined by Fujisawa et al. and Dugdale et al. (4;49), that the mechanical axis should transect the tibial plateau, at 62% of its width, measured from the medial side.

Osteotomy methods

The correction of the knee axis can be obtained with principally different techniques:

1. Closed wedge: a bony wedge is resected from tibia or femur. The gap is the closed to produce either valgus or varus alignment. Stability is typically achieved with staples.
2. Dome: a dome shaped cut in the bone is made to enable the wanted correction.
3. Open-wedge: a single osteotomy is made in the bone. The osteotomy is opened to the aimed correction. Opening of the wedge can be done immediately with intern fixation or with progressive opening of the wedge (hemicallotasis, HCO) with extern fixation.

For many years, the closed wedge has been the predominant method. Coventry, among others, has shown that the method is safe and reliable, especially when one is precautious with overweight patients, and meticulously securing a slight overcorrection (50). It is technically difficult to obtain the correct correction with the closed wedge technique (5), also there is risk of damage to the peroneal nerve when exposing the lateral aspect of the proximal tibia and fibula (51), a complication that can be minimized by resection of the proximal tibiofibular ligament (52), and in spite of a seemingly perfect osteotomy loss of correction can result (53).

Dome-osteotomy (3) seems technically difficult to perform. In spite of technical modifications of the method, and the fact that the method gives intimate bone contact, and thereby theoretically secures safe bony healing, it has not gained much popularity (54).

On the other hand, the open-wedge method is popular, and the method we prefer at our clinic, where we use internal fixation. The procedure does not demand a fibular osteotomy, thus avoiding lateral muscle detachment and minimizing the risk of damage to the peroneal nerve, and, as opposed to the closed wedge technique, in which a wedge is resected, requires only one osteotomy that can be adjusted subsequently during operation, when internal fixation is used, or during the subsequent distraction period, when external fixation is used (9-11).

Nakamura et al. found that open-wedge osteotomy with distraction hemicallotasis is comparable to the dome osteotomy in regards of precision but also secures less changes in length of the patella tendon and inclination of the tibial plateau (55).

Magyar et al. showed that the open-wedge hemicallotasis technique, compared to conventional closed wedge technique, is more precise regarding achieving the planned correction, and is more stable during the healing phase, as measured with RSA. Also, it resulted in shorter hospital stays and sick leave. Shortcomings is that the method is resourceful and bears a high risk of pin-tract infection (14).

In a randomized study comparing the closed wedge technique with the open-wedge technique, Brouwer et al. demonstrated that the open-wedge technique resulted in a significantly more decreased patella, and that the open-wedge technique resulted in increased tibial inclination and closed wedge decreased the inclination (56).

In a similar study Brouwer et al. found, that the closed wedge technique, using a lateral stable, was more precise than the open-wedge technique, using a spacer plate with screws (Puddu Plate®), in terms of achieving the planned correction after one year, and that the open-wedge technique required more frequent removal of hardware. They speculate that the reason for the imprecise correction achieved after one year is a result of loss of correction, maybe because the plate was not sufficiently stable to maintain the obtained preoperative correction (57).

Improved implants

Previous studies have tested the stability of devices for internal fixation most often used in HTO (58-64). Stuart et al. (58) investigated the first generation of the Puddu Plate® (Artrex, Naples, Fla) on frozen cadaver tibias and found it only marginally stable enough to withstand axial loading and insufficient to withstand torsional loadings during gait. Since then, the Puddu Plate has been modified. In the various studies on different implants for internal fixation, load to failure was found to be in the range of 1.6 KN-2.9 KN. Highest failure loads where found for long rigid plates with interlocking screws (TomoFix™, Synthes) (61). Stiffness was found to be in the range of 1349 N/mm – 2425 N/mm, highest for a short spacer plate (61;62). Miller et al. investigated the stability of open-wedge osteotomies performed on Sawbones® using the Dynafix® VS™ Osteotomy System (Biomet) also used in our studies. They found that the stiffness of the construct was 2425 +/- 418 N/mm in axial loading with an intact bony lateral hinge. After breakage of the lateral hinge the stiffness was reduced to 1030 +/- 322 N/mm (61).

Healing of the osteotomy gap

Bony healing of HTO has been investigated in several studies. Electromagnetic field stimulation has been shown to improve the healing of closed wedge osteotomies, by blinded evaluation of roentgenograms (65), ultrasound stimulation accelerated the maturation of the callus in patients treated with opening-wedge HTO by hemicallotasis (66). Mizuta et al. found that a greater frequency of distraction in HTO by the hemicallotasis technique, resulted in higher bone mineral density of the distraction callus, and shorter time with the external fixator (67)

Table 1
References with special emphasis on graft and gap healing

Author	Year	n	Follow-up	Bone substitute	Outcome	Revision	Notes
Hernigou	1987	93	10-13 years	Iliac crest wedges	7 had immediate loss of correction / 21 lost correction during first year / 1-10 years post. op., corrections were generally lost in varus direction.	17 revisions to arthroplasty between 5-10 years – all but one had recurrence of varus	No internal fixation was used in this series. Optimal results with HKA of 183°-186°
Hernigou	2000	245	10 years	Acrylic cement	94% 5 years survival, 85% 10 years survival and 68% 15 years survival. 75% at 183°-186°		A lucent line were noted between bone and cement on radiographs
Koshino	2003	21	79 months	Porous HA wedges and autogenous fibular grafts	No loss of correction No collapses of HA-wedges		HA wedge observed up to 10 years post.op
Staubli	2003	92	9 (3-24) months	None	No implant failures 2 cases of delayed healing resulting in loss of correction	3 arthroplasties performed and 2 recommended, due to progression of arthritis	
Lobenhoffer	2003	213		Local graft in minor corrections/ larger corrections either iliac crest graft or HA/TCP wedges	6 non-unions with implant failure and loss of correction with the Puddu plate (101)		
van Hemert	2004	27	12 months	Porous tricalcium phosphate (TCP) wedges or granules	No los of correction After 12 months		TCP no longer visible in 85% at 12 months
Spahn	2004	85		Iliac crest autograft for corrections >12.5°, Endonbon or no substitute in minor corrections	9 implant failures and 4 severe infections out of 55 operations with the Puddu plate. With the C-plate none of these problems were noted		One case of implant failure resulted in 5° loss of correction after 6 months
Devgan	2003	50	7.5 years	Full thickness iliac crest bone graft	No non-unions One case of early collapse and loss of correction		Plaster cast were used routinely Stables were only used in unstable cases
Studies including histological data							
Koshino	2001	10	23 months	Porous hydroxyapatite blocks	Complete bone covering of HA, 71% filling of pores at 300µm, and no collapses of HA-blocks		HA was considered to be preserved for a long time
Gaasbeek	2005	17	15 months	Porous TCP wedge	Radiological consolidation at 12 months. 13/17 biopsies showed visible TCP, varying stages of bone incorporation		
Dallari	2007	33	12 months	Bone chips/ + platelet gel/ + platelet gel + stromal cells	Platelet gel alone or with stromal cells increased the osteogenic potential and osteointegration after 6 weeks.		All patients had full functional recovery at 12 months

W-Dahl and Toksvig-Larsen found that cigarette smoking did not only delay osteotomy healing but also resulted in higher risk of complications (68), as opposed to their findings that oral snuff, containing nicotine and N-nitrosamines, did not impair the healing in HCO (69).

The open-wedge technique, with internal fixation, leaves a bone gap with a medial opening often exceeding 10mm, which can be left empty or filled with different bone graft materials as suggested by various authors. Autograft secures healing (5;12;15-17) but also includes disadvantages, i.e. limited availability and donor-site morbidity (18). Allograft is another alternative which entails a minor risk of virus transfer (19).

Several synthetic bone substitutes have been introduced for OW-HTO, either alone or in combination with auto- or allograft: Hydroxyappatite (HA), Beta Tricalcium Phosphate and acrylic cement (12;16;17;20-22;70). Still, only one randomized clinical study has been published: Dallari et al. found that platelet gel and the combination of platelet gel and bone marrow stromal cells increased the osteogenic potential of lyophilized bone chips after six weeks. However after 12 month all patients had complete clinical and functional evidence of healing (70).

With or without grafting delayed healing is reported in up to10 % of operations performed. Delayed healing and non-union is associated with implant failure and loss of correction resulting in inferior results (5;12;15-17;20-23) (see table 1 for details). In recent years better implants have improved the primary stability (60;62), but it is still unknown which bone graft materials should be used to obtain optimal osteotomy gap healing.

Bone substitutes

Injectable and remodelable calcium phosphate cements offer supplementary stabilization to osteosynthesis (71-73).

Frankenburg investigated the ICPC Norian® (Synthes), in a metaphyseal defect on canine tibia and femur. Biomechanical evaluation shoved compressive strength superior to normal bone and after eight weeks, the torsional strength was almost that of the intact tibia. Histological evaluation showed slow remodeling – after 32 and 72 weeks, the architecture of the bone was only approaching that of normal bone (24). Ooms studied Calcibon® (Biomet Merck GmbH) in the same manner in diaphyseal defects. He found intimate bone-cement contact, without any fibrous tissue. He also observed slow remodeling, with most of the cement in situ after 24 weeks (25;26). In experimental and clinical studies of fractures of the lateral tibial condyle, augmentation with injectable calcium phosphate cement yielded comparable or better initial stability securing better

final reduction, when compared with bone autograft or allograft. Histologically, slow remodeling was found (27;74-76).

Material and methods

Experimental models

The problems that this thesis focuses on are directly arisen from clinical practice:

- Different bone grafting materials are available but no clear recommendations exist if bone grafting materials should be used, to achieve safe and proper healing of the osteotomy gap for OW-HTO
- Is it of any benefit, to use a bone grafting material that potentially increases the stability of the osteotomy – or does the bone grafting material compromise the osseous healing

We intended the results to be transferable to clinical practice, which is best achieved in a randomized clinical trial. But studying the primary stability of the construct, including a (potentially) destructive test, was not possible in a clinical trial.
We therefore used two experimental models:

1. An in vitro biomechanical model, using cadaver and composite tibias, testing the primary stability of the OW-HTO construct.
2. A clinical randomized study testing the in vivo influence of different bone grafting materials on clinical, radiographic, and histological outcome.

Bone graft materials

Accordingly we wished to test the performance of three different bone grafting materials that we used in daily clinical practice:

Injectable calcium phosphate cement (Study I and II)

Fig. 2a: Injection of ICPC

We used Calcibon® (Biomet Merck GmbH) which is a synthetic, biodegradable, calcium phosphate based bone substitute. It is intended for filling of metaphyseal, cancellous bone defects. The material is mixed during the operation from a liquid and a powder part consisting of 58 % α-TCP (Tri Calcium Phosphate), 8.5 % PHA (Precipitated Hydroxyappatite), 25 % CaHPO4 (Calcium Phosphate) and 8.5 % CaCO3 (Calcium Carbonate). The resulting paste is applied directly and hardens at body temperature **(fig. 2a)**. The chemical composition and crystalline structure of the cured material mimic the mineral part of natural bone. The compressive strength of the material increases during the hardening process, and after 6 hours it is comparable to cancellous bone. The final compressive strength is reached after 3 days and is up to 60 MPa (25;26;77).

Local bone autograft (study II)

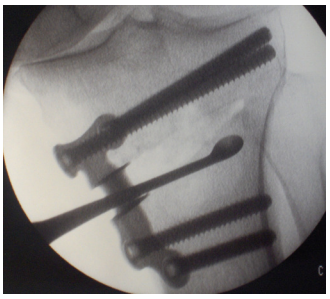


Fig. 2b: Local bone autograft

Using a curette, the cancellous bone from the two adjacent cut surfaces was scooped out in the osteotomy defect creating a loosely woven bone network serving as scaffold in the bone gap, potentially accelerating gap healing (fig. 2b). The method is easy to apply and requires no special instruments. The use of local bone as a bone grafting material in open-wedge osteotomies has been described by Lobenhoffer et. al. as "local cancellous bone graft" however without further specifying the procedure (12).

Iliac crest bone autograft (study II)

Fig. 2c: The Accumed bone graft harvesting system

Cancellous bone, corresponding to the volume (V) of the osteotomy, was harvested from the iliac crest using the Accumed® Bone Graft Harvesting System (Acumed®, Oregon, USA). The system is minimally invasive enabling harvest of several milliliters of milled bone (fig. 2c).

Study design

Study I – biomechanical study

Two biomechanical studies were conducted to test displacement and load to failure under axial loading.

Displacement study: eight pairs of cadaver tibias (left and right) were tested to investigate displacement after cyclic, axial loading. DEXA scan was carried out before the operation for comparison of bone mineral density (BMD).

Load to failure study: seven pairs of composite tibias (left/left) were tested to investigate axial load to failure.

In both studies specimens were randomly assigned to either ICPC or empty gap. All specimens had the same osteosynthesis of the osteotomy.

Study II – clinical randomized study

A randomized controlled trial was carried out with 45 patients who had an open-wedge osteotomy performed. After opening and osteosynthesis of the osteotomy, sealed envelopes was opened in the operating theater, revealing the random assignment to either of the intervention groups:

1. Local cancellous bone autograft.
2. Iliac crest bone autograft.
3. Injectable calcium phosphate cement (Calcibon®)

The patients followed the same rehabilitation protocol including walking with crutches and limited weight bearing (20kg), with the knee in a hinged brace allowing free flexion in the knee joint, the first six postoperative weeks. Thereafter full weight bearing was commenced

The planned follow-up included examinations after six weeks, 3, 12 and 24 months postoperatively. After 12 month, the internal fixation was removed during a planned one-day admission.

The study was approved by the local ethics committee and registered at Clinical Trials Gov.

Materials

Cadaver bones (study I)

The cadaver bones were pairs of tibias supplied by the program of "Body Donation to Medical Science, Institute of Anatomy, University of Aarhus". The bones were preserved in glycerin, formalin, and 96% alcohol. The specimens were stripped of skin and muscles, and fibula was removed. All specimens had periosteum and pes anserinus in place.

The specimens were subjected to DEXA scan before the operation.

Mean age of the donors were 73 years and 8 month. Preoperative BMD measurements of the central, proximal part of the tibia were performed to test for intra-individual side-to-side variability in the bone mineral density (BMD: control-group = 0.41g/cm² (95% CI, 0.3-0.5), ICPC-group = 0.36g/cm² (95% CI, 0.30-0.41), P-value = 0.19, paired t-test).

Composite bones (study I)

The composite bones were fourth generation composite tibia (Sawbones®, Pacific Research Laboratories, Inc., Vashon, USA) which have been validated for biomechanical testing (78).

Patients (study II)

Patients included in the clinical trial were all candidates for medial open-wedge osteotomy: young (18 – 65 years) patients with early stages of osteoarthritis (Ahlbeck gr. 0-2) of the medial knee compartment and a varus deformity. Excluded were patients with BMI>35, patients with previous intraarticular fractures of the knee, degeneration to the lateral compartment, patients medicated with NSAID or steroids, and patient's unwilling to join the study (missing informed consent).

In the period 10th December 2004 to 12th June 2006 71 patients had a corrective open-wedge osteotomy performed at our clinic. Of these, 61 were unilateral medial open-wedge. 12 patients were excluded: 4 because of too high BMI, 3 because of intercurrent disease and 5 rejected participation. 49 patients accepted to be included in the project and signed informed consent. Four were excluded after inclusion and signed informed consent but before operation: one had rapid progression of arthritis necessitating total knee replacement, one was operated at another clinic, one was excluded because of interim competing disease and one withdrew consent to participation. Thus 45 patients were included and randomized, see table for patient characteristics.

Table 1
Patient characteristics

	All n = 45	Local bone autograft n = 15	Iliac crest autograft n = 15	Calcibon n = 15
Sex (Women/men)	11 / 34	4 / 11	4 / 11	3 / 12
Age mean (years)	48.0	50.5	47.8	45.6
SD	8.1	7.8	9.6	6.1
Weight mean	86.6	83.6	86.0	90.0
SD	12.7	13.2	14.6	9.8
BMI mean	27.7	27.3	27.4	28.3
SD	3.5	3.3	4.0	3.2
Smokers	16/45	7/15	4/15	5/15
Ahlbäck gr.	1.3	1.1	1.4	1.3
Range	1- 3	1 - 2	1 - 3	1 - 3
HKA mean (°)	175	174	177	175
Range	168 - 182	168 - 179	171 - 182	168 - 182
Peroperative Fracture None/undisplaced/displaced	32/10/3	9/5/1	13/1/1	10/4/1
Gap size (mm)	10.1	10.8	8.8	10.7
Range	5 – 17.5	6.25 – 17.5	5 - 15	6.25 - 15

Operation

Osteotomy and osteosynthesis

Basically the same osteotomy technique and equipment were used both in the clinical trial and the biomechanical study:

Patients were operated in supine position using a tourniquet. Vertical incision over the proximal, medial aspect of tibia was used. Pes anserinus and periosteum was mobilized and deflected posterior to allow for the oblique infracondylar osteotomy. The osteotomy was initiated with saw and completed with osteotome. Opening of the osteotomy was performed with bone distractor, and fixation was performed with a titanium spacer plate with non locking 6.0 mm titanium screws (Dynafix® VS™ Osteotomy System (Biomet Merck GmbH)).

To secure that a standardized osteotomy was performed on the composite bones, a custom moulded cast was used for each specimen. In the biomechanical study all specimen had a 10-mm open-wedge osteotomy.

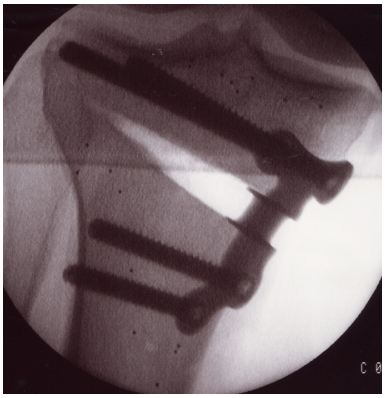
All operations were aiming at a mechanical axis transecting at the 62%-point of the medio-lateral diameter of the proximal tibial plateau, as this is the axis we usually strive to achieve, aproximating 3º-5º of valgus (4;49).

Grafting procedures (fig. 3)

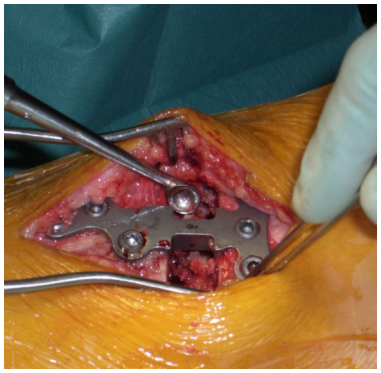
1. Calcibon (study I and II): The cement was mixed and injected into the osteotomy defect with a syringe. In the biomechanical study 15g of Calcibon were used in each gap. In the clinical study enough paste was mixed to enable macroscopic filling of the osteotomy. The handling directions of the manufacturer were followed
2. Local bone autograft (study II): Using a curette, the cancellous bone from the two adjacent cut surfaces was scooped out in the osteotomy defect creating a loosely woven bone network.
3. Iliac crest bone autograft (study II): Cancellous bone, corresponding to the volume (V) of the osteotomy, was harvested from the iliac crest using the Accumed® Bone Graft Harvesting System (Acumed®, Oregon, USA). The system is minimally invasive enabling harvest of several milliliters of milled bone. The height (h) and diameter (2*r) of the osteotomy, considering the gap a wedge, was used to estimate the gap volume:

$$V \sim \pi * r^2 * h/2$$

Fig. 3
Grafting procedures



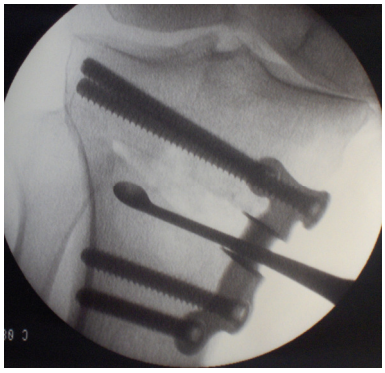
Empty osteotomy before grafting



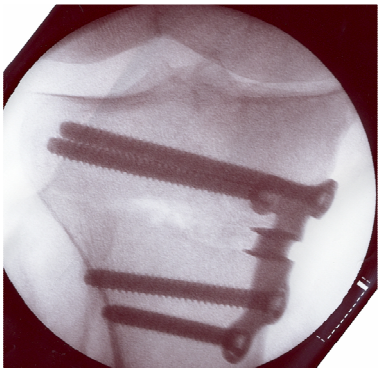
Peroperative local bone autograft procedure

Accumed bone graft system for harvest of iliac crest bone autograft

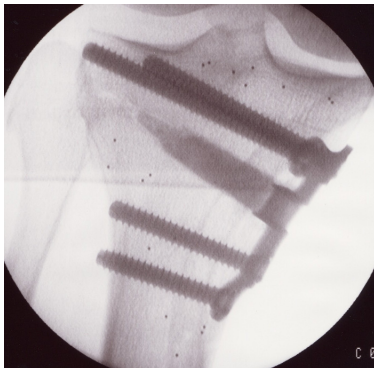
Calcibon powder and liquid



Peroperative fluoroscopic picture of local bone autograft



Peroperative fluoroscopic picture of iliac crest bone autograft



Peroperative fluoroscopic picture of osteotomy grafted with Calcibon

Biomechanical testing of cadaver and composite tibias

Setup

First the mechanical axis was marked. The proximal tibial joint surface was prepared for cement-fixation by drilling three anchorage holes (6mm diameter) and then rigidly fixed in polymethylacrylat (Refobacin® Bone Cement R). Correct orientation exactly on the planned mechanical axis was secured by centralizing the distal and proximal points of passing of the mechanical axis in a clamp during cementation. After curing of the cement on the proximal end, the specimens were shortened leaving the proximal 13.5cm. Finally the distal part was potted in bone cement, and the specimens were ready for test in an Instron Universal Material Testing Machine (fig. 4).

Figure 4

Stepwise preparation of specimen, from left to right:

Preparation of joint surface, alignment, potting while maintaining alignment, shortening and finally the specimen ready for test in the material testing machine

Test-procedures

Study 1, cadaver bones, displacement after cyclic test

Starting with a maximal load of 200N for ten cycles, increasing maximal loads were applied at 750N and 1500N for each ten cycles. Then 100 cycles with a maximal load of 2250N were performed. The 2250N corresponds to the load on the knee at normal walking for a person of 75kg (3 x the person's weight (79)).

Test parameters:

- Unloaded displacement at the start of the first and last full cycle with 2250N
- Loaded displacement at the conclusion of the first and last full cycle with 2250N
- Stiffness of the construct in the first and last full cycle with 2250N
- Amplitude of the first and last full cycle with 2250N

Study 2, composite bones, load-to-failure test

The specimens were loaded at a ramp speed of 20mm/min until a maximal load of 20kN. Data were recorded every 10N. Failure was defined as the point at which the first reduction in loading occurred (63).

Test parameters (63;80):

- Failure load, defined as the first peak on the load-displacement curve
- Stiffness, defined as the maximum slope of the load-displacement curve before failure
- Energy absorption, defined as the area under the load-displacement curve before failure

Data were recorded on a pc as data points with corresponding loads (Newton) and displacement (mm). Calculation, and identification of the parameters, was auto generated in SPSS.

RSA

Basic principles

RSA is a highly accurate method of quantifying minute movement in the skeleton. It was introduced by Selvik (81) and has been used in open-wedge osteotomies, both in experimental (82) and clinical studies to determine motion of proximal tibia after HTO (83;84).

The method is based on the principle that spherical tantalum markers project on the x-ray film which in combination with a calibration cage, defining a "laboratory coordinate system", enables calculation of 3-D coordinates of the markers. A minimum of three non-collinear spherical tantalum markers form a rigid body representing a segment, i.e. extremity, bone or prosthesis. Thus motion between two rigid bodies can be detected between two examinations. Micromotion can be divided into two types – migration and inducible displacement.

Migration reflects the gradual motion over time. Thus migration is the relative motion between two supine examinations performed at different time points.

Inducible displacement is load induced micromotion. One-leg standing RSA examinations were carried out immediately after the normal supine examination. The relative movement between these two examinations thus reflected the current stability of the osteotomy construct (85).

Preparation for RSA

In the present study the first rigid body represented the proximal articular bone segment above the osteotomy, and the second rigid body represented the distal bone segment below the ostetotomy (fig. 5).

Insertion of spherical tantalum markers was done after completion of osteosynthesis. In each segment we placed four to nine, 0.8 and/or 1.0 mm tantalum markers for ease of identification.

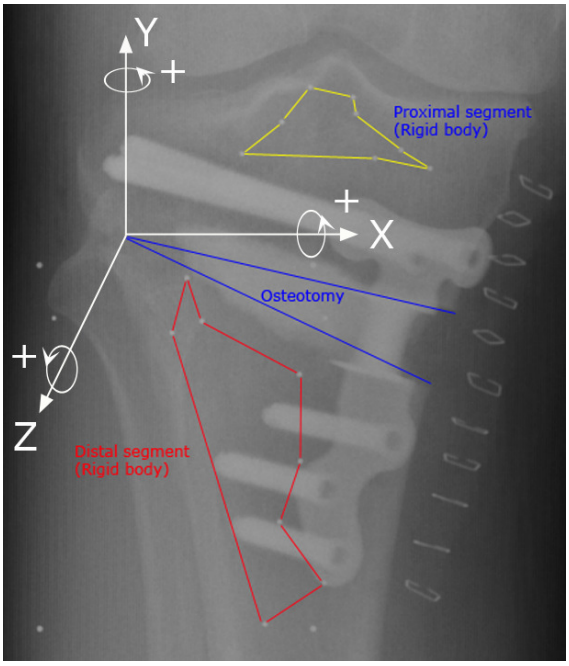


Fig. 5

Marking of tantalum spheres defining proximal rigid body (yellow) and distal rigid body (red), and 3-D coordinate system with arrows showing direction of positive rotations around axes

RSA examination

RSA examinations were performed:

- 1-3 days postoperatively in supine position
- 3 months postoperatively in supine postition
- 12 months postoperatively in supine position, before hardware removal
- Immediately after hardware removal in supine and one-leg standing position
- 24 months postoperatively in supine position

We used the bi-planar cage 10 (RSA Biomedical, Sweden) in combination with mobile x-ray tubes. Synchronous x-ray recordings were performed with patients leg aligned in the calibration cage in the same manner at each examination (fig. 6).

Fig. 6
RSA examinations in supine (left) and one-leg standing positions (right).
X-ray tubes can move freely enabling uniform alignment of the bi-planar cage.
After alignment of cage the patient's knee is positioned "inside" the cage in the same manner at all examinations.

RSA images

Analog images where scanned in UmRSA Digital Scan on an Umax Power Look 2100 XL scanner. Spatial resolution where set to 300 DPI, scanning gamma correction (gray-scale) where set to 2.2 or 3.0 in dark images.

Digital images were transmitted and imported with use of the UmRSA DICOM Link with an image resolution of 254 DPI, in DICOM 3.0 format. UmRSA V. 6.0 software was used for measuring of images and calculation.

Rigid body configuration and stability

For accurate assessment of micromotion it is of paramount importance that the configuration of the rigid bodies is optimal and stable. This means that the tantalum markers should be well scattered (non-linear) in all three dimensions and stay in the same position. The degree of scattering is given by the condition number (CN), where high numbers indicate poor scattering (86). The stability, of the tantalum markers constituting a rigid body, is given by the mean error of rigid body fitting (ME), representing eventual relative changes of the rigid body between two examinations – consequently a high ME implies a unstable rigid body. Following the guidelines given by Valstar et.al (87), we excluded examinations with CN above 150, and ME above 0.25.

RSA parameters

The motion of the proximal articular segment was measured relative to the distal segment. Migration is reported as maximal total point motion (MTPM) or as rotations around and translations along the 3 axes (X, Y, Z). MTPM represents the length of the translational vector of the marker that moved the most between two examinations. Several problems are associated with MTPM: It is very sensitive to loose markers, it is not necessarily the same marker that moved the most between different examinations, and the position of the measured marker is not the same from patient to patient making comparison incorrect.

To address these problems we therefore instead used the MTPM translational vector of fictive points representing the tibia eminences. This implies that easy identifiable (anatomical) landmark(s) is marked in one pair of images for each patient. The points are given 3-D coordinates relative to the rigid body representing the segment one wish to study. Thereafter, at every examination, the "fictive" points simply "follow" the segment, and the translational vector (MTPM) can be calculated.

Rotation of the rigid body, in the proximal segment, around the 3 axes (X, Y, Z) is expressed with (+) and (-) for positive, respectively negative rotation. Positive rotation around the X-axis results if the rigid body tilts anteriorly, positive rotation around the Y-axis equals internal rotation, and rotation around the Z-axis results in valgus (+), and varus (-).

The translation values represent translation of the center of gravity of the rigid body along the 3 axis, X-axis being medial-lateral, Y-axis being proximal-distal and the Z-axis being anterior-posterior. Rotation and translation results are all presented as right sided results, meaning that the results for left sided osteotomies has been transformed to right sided.

Precision of the method was found as the measuring error of scanned images from 9 double examinations on 9 randomly chosen patients. The patients stepped down from the examination table between examinations.

Clinical scores

Knee injury and osteoarthritis outcome score (KOOS) is a clinical score intended for evaluation of follow-up of physically active patients after knee injury (88;89) and the consequences of knee osteoarthritis (90;91). The score is sensitive to changes in symptoms and function in both the immediate posttraumatic/postoperative stage as well as regarding the long term consequenses after injury and osteoarthrtitis, and it is therefore useful in the follow-up after open-wedge osteotomies (92). The questionnaire is self administered and comprises 5 subscales: Knee related symptoms (symptom), pain, sport & recreation (sport), activity of daily living (ADL), and quality of life (QOL). On each of the subscales 100 points equals zero problems whereas 0 points equals extreme problems (93).

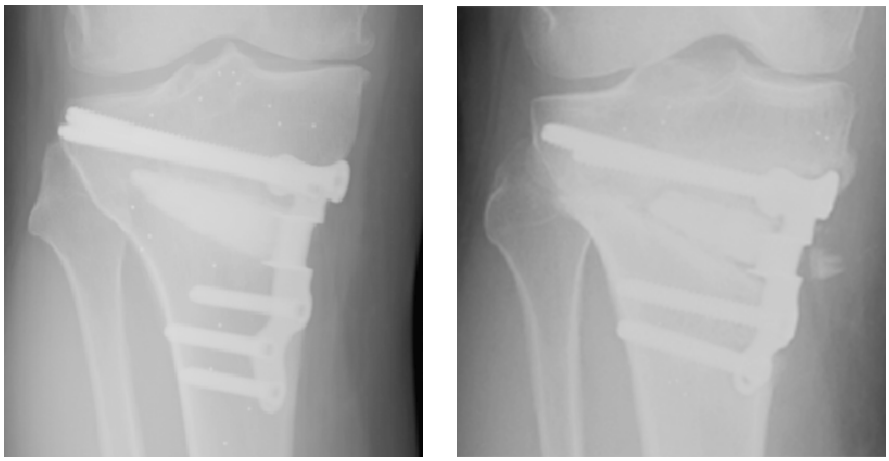
Roentgen

Before and two years after operation, arthritis were graded according to Ahlbäck (94) on radiographs with the patient in standing position. Likewise, on simultaneous standing position radiographs of the hip, knee and ankle, valgus/varus deformity was assessed with the medial hip-knee-ankle angle (HKA angle, varus <180°), as described by Moreland (95).

Bone filling of the osteotomy was estimated by judging whether or not the osteotomy was filled in each one third from lateral to medial.

In the ICPC group it was noted whether or not cement was present and whether demarcation was present around the cement, or if the cement seemed to integrate with the bone.

Fig. 7
X-rays of ICPC osteotomies with well integrated ICPC (Left) and demarcated ICPC (Right)



Biopsies for histological analysis of gap healing

Sampling of biopsies

Biopsies were harvested at time of hardware removal immediately after the 12 month control.
After plate and screws were removed, 6mm cylindrical core biopsies crossing the osteotomy were harvested with a 6mm trephine under fluoroscopic guiding. To secure uniform sampling region the osteotomy were acquired through the proximal of the distal screw holes, at an angle of approximately 45 ° on the longitudinal axis in the A-P plane, and central and parallel to the longitudinal axis in the side plane.
Until preparation the biopsies were kept at -20 °.

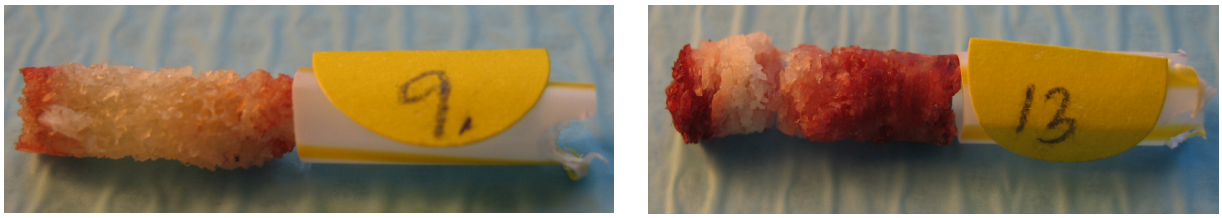


Fig. 8
Autograft bone specimen (left) and Calcibon (right)

Specimen preparation

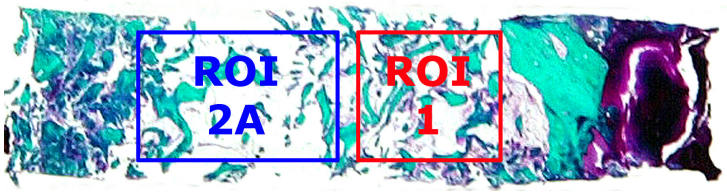
Thawed biopsies (fig. 8) were dehydrated in graded ethanol (70-100%) containing basic fuchsin. After dehydration each biopsy was embedded in methyl methacrylate. Using vertical sectioning technique (96;97) four 60-100 µm central histological sections were cut from each biopsy with a microtome. The sections were surface counterstained with 2 % light green for 2 min, rinsed and mounted on glass (98). This preparation provided red staining for non-calcified tissue and green staining for calcified tissue. Different bone types (woven and lamellar bone) were discriminated by their morphological characteristics: Lamellar bone was defined by a highly organized lamellar and linear structure with flattened lamellar-oriented oval cells. Woven bone was characterized by a less organized structure with rounded cells and without any lamellar structure.

Histomorphometric analysis

Quantitative histomorphometry was performed using the stereological software newCAST (Visiopharm A/S, Hørsholm, Denmark). Regions of interest (ROI) were defined by an independent observer. Delineation of the regions was done with the aid of the software.

Autograft bone groups

ROI 1: Trabecular bone just adjacent to medial, metaphyseal, cortical bone.
ROI 2A: Osteotomy gap.



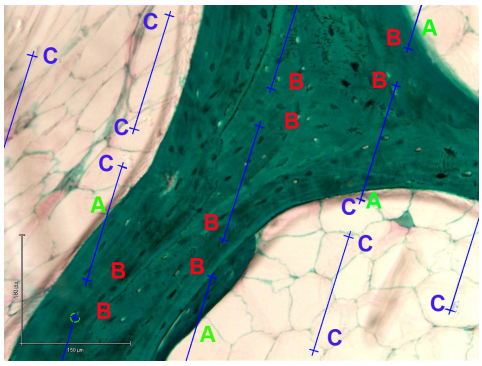


Fig. 9
Regions of interest (left) and point and line grid (right)
Each cross/point overlaying a specific tissue (B and C), represents an area. The sum of point's ads up to the area of the specific tissue from which tissue volume fractions can be calculated. The lines has a given length and by counting the intersections with bone surface (A) the trabecular thickness can be calculated.

In the regions defined, initially, volume fractions of woven bone and lamellar bone, fibrous tissue and marrow space were quantified by point-counting technique.

$$\text{Tissue volume fractions} = \Sigma\text{Points tissue}/\Sigma\text{Total points}$$

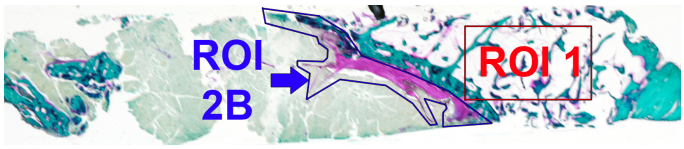
With line-interception and point counting of the trabeculae, the mean trabecular thickness was estimated as the reciprocal value of BS/BV (Fig. 3b) (99).

$$\text{Trabecular thickness} = 2/2*(p/l)*(\Sigma\text{Bone-intercepts}/\Sigma\text{bone-points})$$

Calcibon group

ROI 1: Trabecular bone just adjacent to medial, metaphyseal, cortical bone.

ROI 2B: Bone-cement interface.



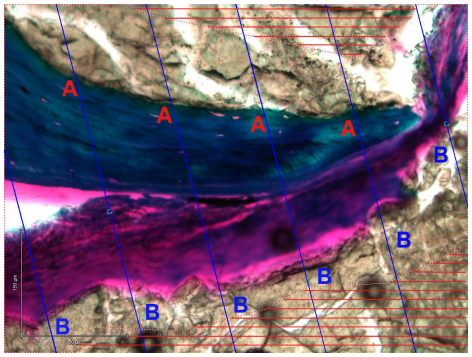


Fig. 10
Regions of interest (left) and line grid (right)
The lines intersecting the calcibon interface with either bone (A) or fibrous tissue (B) are counted. From this, surface fractions of tissue-covering can be calculated.

In ROI 1 the same parameters were used as in the bone specimens.

The surface area fractions of bone-covered cement, and non bone-covered cement, (primarily fibrous tissue), were quantified with line-interception technique (97).

$$\text{Surface fraction} = \Sigma\text{Tissue intercepts}/\Sigma\text{Total intercepts}$$

Statistics:

Study I – Biomechanical study

The study was designed to find an increase in load to failure, and a decrease in displacement of 25% with expected standard deviation of 15% and a risk of type 1 error of 5% and a power of 80%. To find such a difference, seven specimens were needed in each group.
Corresponding data points of load and displacement were recorded, and from these data, load-displacement curves, and biomechanical parameters were auto generated.
Means and standard deviations were calculated. Difference between groups in load-to-failure, was compared with Cox regression since not all of the ICPC specimens failed. For the rest of parameters, differences between groups were tested with paired t-test and Students t-test.

Study II – Randomized clinical trial

Our primary outcome in the clinical study was migration after one year. A simple way to estimate this is the MTPM. Before the study we estimated a clinically relevant different to be 1 mm. Thus the study was designed to find such a difference with three groups and an expected standard deviation of 0.5mm and a risk of type 1 error of 5% and a power of 80%. To find such a difference, six patients were needed in each group. To accommodate for eventual dropouts we included 15 in each group (3 x 15).

RSA parameters

MTPM, were tested with non-parametric Kruskal-Wallis's test. Secondary outcomes: rotations and translations after one year were tested with ANOVA with robust variance estimation. Differences in KOOS subscores between groups were tested with Kruskal-Wallis's test.

Histomorphometric parameters

Means and standard deviations were calculated. Differences between groups were tested with one-way ANOVA in ROI 1. In ROI 2 only the two bone groups (local graft and iliac crest graft) were compared with t-test, since the majority of ICPC was still present and therefore defined the ROI.

In all studies a p-value below 0.05 was considered significant.

Summary of results

Biomechanical study

Cadaver bones, displacement after cyclic test

The loaded displacement, of the empty gap group, was nearly twice the size of the displacement found fore the ICPC-group ($p = 0.006$) after completion of the first full cycle, and stiffness was found to be more than four times higher in the ICPC-group ($p < 0.001$). After 100 cycles, ICPC showed a stabilizing effect on the construct with significantly higher stiffness, lower loaded and unloaded displacement values, and lower amplitudes than the control group (fig. 11 and table 2).

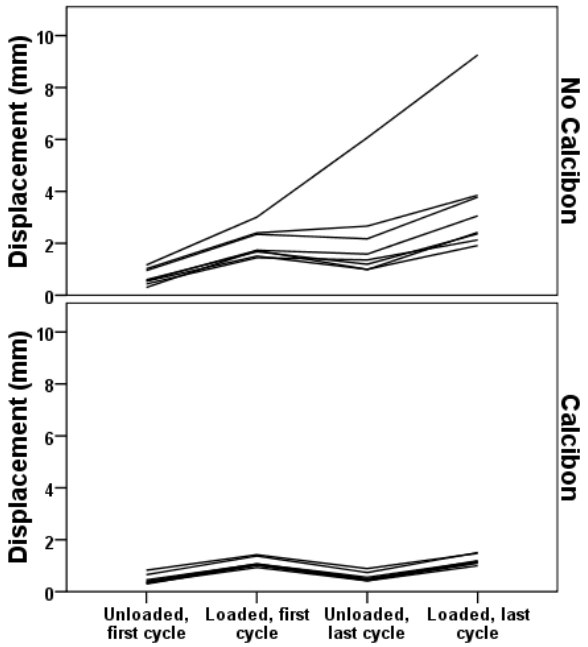


Fig. 11
Displacement after cyclic loading. Each line showing displacement at the observation points for each specimen in the two groups.

	Control (N = 8)		Calcibon (N = 8)				
	Mean	**SD**	**Mean**	**SD**	**Mean diff.**	**95 % CI**	**p-value**
Displacement (mm)							
Unloaded 1st cycle	0.70	0.31	0.46	0.19	0.24	-0.10 – 0.58	0.138
Loaded 1st cycle	1.98	0.55	1.12	0.18	0.86	0.33 – 1.40	0.006
Unloaded Last cycle	2.13	1.70	0.56	0.17	1.57	0.10 – 3.05	0.040
Loaded Last cycle	3.60	2.40	1.21	0.18	2.38	0.34 – 4.42	0.028
Stiffness (kN/mm)							
First cycle	3.1	0.7	14.7	5.3	11.6	7.2 -16.0	0.000
Last cycle	5.2	2.2	51.6	41.5	46.4	11.8 -81.1	0.016

Table 2 Displacement after cyclic loading, cadaver bones

Composite bones, load-to-failure

Failure occurred before 20kN in all of the control specimens (mean 4.2, median 2.8kN), but only in five of the ICPC specimens (mean 15, median 17kN). As two of the ICPC specimens did not fail, survival analysis vas also carried out, revealing a significant difference in survival until load-to-failure with a Hazard Ratio of 0.1 (p = 0.005).

Still the failure-load noted in the control group exceeded the load expected to be encountered during normal walking of a 75kg person (approximately three times body weight – 2.25kN) (fig. 12 and table 3).

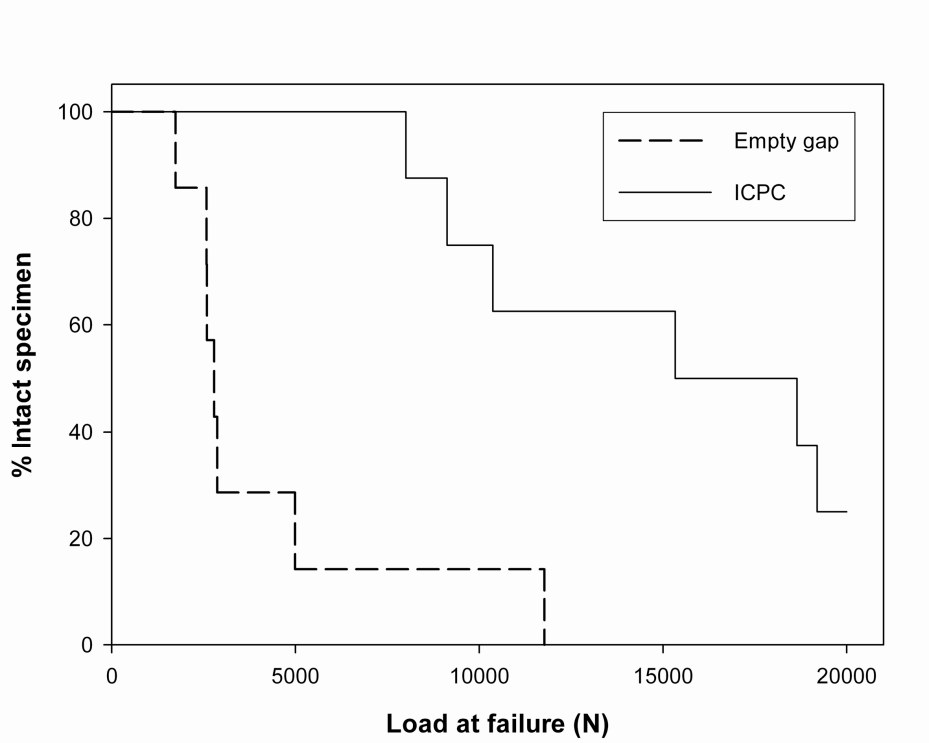


Fig. 12
Load-to-failure, composite tibias

	Control (N = 7)		Calcibon (N = 8)				
	Mean	**SD**	**Mean**	**SD.**	**Mean diff.**	**95 % CI**	**p-value**
Load (kN)	4.2	3.4	15.1	5.1	10.9	5.9 – 15.9	0.000
Stifness (kN/mm)	4.8	0.9	11.6	1.4	6.8	5.5 – 8.1	0.000
Energy absorbtion (kN*mm)	3.8	6.0	24.3	22.0	20.5	1.9 – 39.0	0.035

Table 3
Load-to-failure, composite tibias

Randomized clinical study

In the study period one patient (Calcibon group) died before the one-year control of unrelated causes. Another patient (iliac crest group) missed the one year control before hardware removal as the hardware was removed at another hospital, and one patient followed the study plan until the one year control after which he did not want to complete the study (including refusal of hardware removal) because of other disease.

RSA

Four set of images were excluded because of too high (>0.25) ME of rigid body fitting (loose markers and/or poor image quality). Furthermore another six set of images was excluded because of too high condition number (>150).

MTPM (mm) after one year	N	Mean	SD	P-value
Local bone autograft	12	1.90	1.37	0.121
Iliac Crest bone autograft	9	1.35	1.20	
Calcibon	12	1.11	1.11	

Table 4
MTPM after one year

After one year only minor non significant migrations were found in all groups. MTPM was highest for the local bone autograft group and lowest for the Calcibon group (table 4). Mean rotations and translations after one year were all below one degree for the rotations and one millimeter for the translations regardless of bone grafting material (table 5).

	Local bone autograft		Iliac crest autograft		Calcibon		P-value
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
X-rotation	-0.87	-1.66 - -0.08	-0.76	-1.82 - 0.29	-0.65	-1.16 - -0.15	0.87
Y-rotation	0.27	-0.51 - 1.06	0.34	-0.11 - 0.79	0.05	-0.28 - 0.38	0.49
Z-rotation	-0.01	-0.98 - 0.96	0.04	-0.60 - 0.67	-0.67	-1.44 - 0.11	0.28
X-translation	-0.13	-0.90 - 0.64	-0.17	-0.73 - 0.40	0.35	-0.03 - 0.74	0.19
Y-translation	-0.77	-1.40 - -0.14	-0.64	-1.15 - 0.14	-0.54	-0.98 - -0.09	0.80
Z-translation	-0.59	-0.97 - -0.21	-0.46	-0.98 - 0.07	-0.37	-0.64 - -0.10	0.58

Table 5
Rotations and translations of proximal segment after one year

Studying MTPM over time (fig. 13) all three groups displayed most of their migration within the first three months. Thereafter slightly different, non significant, migration patterns were displayed: Calcibon was more stable in the first three months but migrated discrete to the two year control. The local bone autograft group migrated the most during the first year after which it seemed to stabilize. The iliac crest bone autograft group stabilized after the 3 month control.
Inducible displacement after hardware removal, one year postoperatively, displayed average movement below our detectable limit for MTPM and maximum movement below 1mm, indicating that the osteotomies had stabilized and thus healed

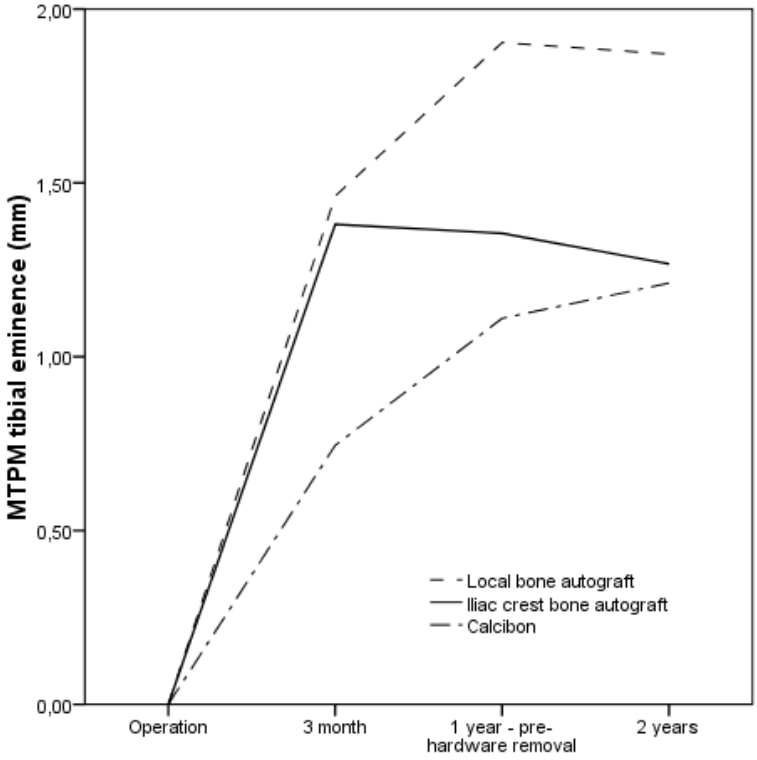


Fig. 13
Migration displayed as mean MTPM after 3 months, 1 and 2 years postoperatively

Radiographic results

The radiographic results reflected the RSA results, namely that the obtained correction, ass measured after 3 months, remained the same throughout the study period.
Radiographic progression of arthritis ceased, with an overall improvement in the Ahlbäck score.
A non significant relationship was found between radiographic demarcation of the ICPC and fibrous tissue covered surface fraction of the ICPC.

KOOS

Clinically, improvements were seen in all subscores after one year, especially in the ADL, pain-, and sport scores. The Calcibon group revealed the lowest (worst) scores in all subscores at all time points apart from ADL after 6 weeks where the iliac crest group had the lowest score. Only the QOL score at two years for the Calcibon group differed significantly from the local graft group ($p = 0.047$) (table 6).

		Visit									
		Inclusion		6 weeks		3 months		12 months		24 months	
Subscale	Group	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean SD	N	Mean (SD)
Symptom	Local	15	61 (16)	15	70 (17)	14	68 (19)	15	78 (19)	14	74 (25)
	Iliac crest	15	66 (17)	14	72 (16)	15	67 (14)	15	75 (18)	14	73 (22)
	Calcibon	15	61 (17)	15	61 (23)	15	60 (21)	14	69 (20)	14	67 (17)
Pain	Local	15	52 (15)	15	70 (18)	14	66 (16)	15	79 (20)	14	78 (23)
	Iliac crest	15	53 (14)	12	68 (19)	15	56 (16)	15	70 (21)	14	67 (24)
	Calcibon	15	49 (15)	14	64 (21)	15	56 (24)	14	66 (27)	14	63 (27)
ADL	Local	14	58 (16)	14	65 (15)	14	68 (16)	15	83 (18)	14	80 (23)
	Iliac crest	15	58 (15)	9	57 (17)	15	63 (17)	15	74 (18)	14	70 (24)
	Calcibon	14	58 (20)	14	60 (21)	15	62 (22)	14	69 (27)	14	67 (26)
Sport	Local	15	26 (16)	9	9 (11)	14	29 (19)	15	52 (26)	14	53 (25)
	Iliac crest	13	20 (16)	10	15 (24)	15	25 (18)	14	42 (28)	14	42 (28)
	Calcibon	14	22 (13)	14	11 (16)	14	21 (21)	13	35 (31)	14	38 (32)
QOL	Local	15	34 (18)	14	35 (13)	14	38 (15)	15	62 (23)	14	66 (26) *
	Iliac crest	15	32 (14)	11	32 (16)	15	42 (18)	15	55 (29)	14	50 (27)
	Calcibon	15	30 (14)	15	30 (20)	15	35 (20)	14	39 (22)	14	40 (25) *

Table 6
KOOS scores

Histomorphometric study

Forty-two biopsies were obtained (one had the plate removed at another hospital, one rejected plate removal and one had died of unrelated causes), six biopsies were of inferior quality, i.e. fragmented, broken or with unidentifiable ROI's, which left thirty-six well preserved biopsies suitable for histomorphometric evaluation.

ICPC

In the osteotomy gap of all of the ICPC samples, large amounts of ICPC were still present. The biologic active surfaces were covered with varying grades of fibrous tissue or bone, varying from 100 % bone cover to 95 % fibrous covering, n fact more than half the specimen had a fibrous tissue covering of 55 % (table 7 and fig. 14).

Case Number	Bone covered Fraction	Fibrous covered Fraction	Demarcation of ICPC
1	100	0	No
2	100	0	No
3	100	0	No
4	98	2	No
5	69	31	Yes
6	45	55	Yes
7	40	60	No
8	39	61	No
9	39	61	No
10	19	81	Yes
11	5	95	Yes
N	11	11	
Median	45	55	
Max	100,00	95	
Min.	5	0	

Table 7

Bone and fibrous tissue covered fractions of ICPC surfaces

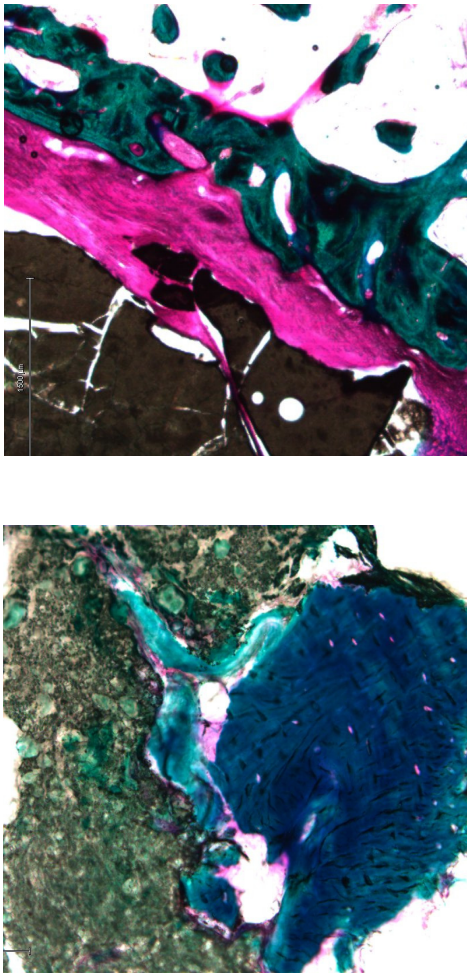


Fig. 14

Dense fibrous tissue cape covering the cement (top right), and bone remodeling and cement resorbtion (bottom right)

Bone autograft groups

Generally remodeled bone was found (exept from in the ICPC osteotomy gap), the vast majority of bone tissue being lamellar trabecular bone. In the bone autograft groups only sparse amounts of fibrous tissue was present throughout. In the two autograft bone groups the gap had healed to the same quality regarding BV/TV and trabecular thickness (Table 8).

	Local graft (N = 13)		Iliac crest graft (N = 12)				
	Mean	**SD**	**Mean**	**SD**	**Mean diff.**	**95 % CI**	**p-value**
ROI II, "Defect"							
BV/TV (%)	24.1	12.7	27.7	9.5	3.5	-5.8 -12.9	0.443
Trabecular thickness (µm)	114	58	97	40	17	- 24 - 60	0.400

Table 8
Bone volume fractions (BV/TV), and trabecular thickness in the osteotomy gap after one year

When comparing the superficial trabecular region (ROI 1) below the osteotomy gap, no significant differences were found in BV/TV and trabecular thickness between all three groups (table 4). However, the total mean trabecular thickness of the osteotomy gap (106µm, SD 49, n = 24), of the two autograft bone groups, was significantly slender than the total mean trabecular thickness (139 µm, SD 57, n = 36), of the adjacent trabecular bone of all three groups (p = 0.025). Though, at group level the differences were not statistically significant.

ROI I - "Original trabecular bone"		**N**	**Mean**	**SD**	**95 % CI**	
					Lower Bound	**Upper Bound**
BV/TV (%)	**Control**	13	29.1	14.1	20.6	37.6
	Cristagraft	12	24.6	8.2	19.4	29.8
	Calcibon	11	34.9	10.0	28.2	41.7
Trabecular Thickness (µm)	**Control**	13	132	61	95	169
	Cristagraft	12	127	29	96	158
	Calcibon	11	159	60	119	199

Table 9
Bone volume fractions (BV/TV), and trabecular thickness of adjacent trabecular bone after one year

Discussion

One of the major goals of improved methods for OW_HTO is to achieve safe healing and fast recovery with full weight bearing immediate postoperatively: Following osteotomy with the hemicallotasis technique where immediate full weight bearing is allowed, W-Dahl et al. found that large improvements in clinical outcome (KOOS) occurred already during the immediate postoperative period (92).

The aims of the present thesis were to investigate factors influencing the bony healing process after open-wedge high tibial osteotomy (OW-HTO), especially the mechanical and biological effects of different bone grafting materials as supplement to internal fixation.

In vitro, injectable calcium phosphate cement (ICPC) improved the primary stability of the OW-HTO construct in terms of displacement after cyclic loading, and load-to-failure (I). However the positive effect could only partly be reproduced in the clinical trial where only minor migration measured with RSA were found regardless of bone grafting material, though with ICPC displaying the least migration (II). More seriously, mixed soft tissue responses, with fibrous tissue covering of the ICPC surface were noticed in biopsies retrieved after one year (III). Also clinically, no benefits were found. On the contrary the ICPC group displayed generally worse clinically scores than the two bone autograft groups (II).

The overall aim was to optimize the healing of the osteotomy gap, facilitating immediate full weight bearing. In the randomized clinical study, 6 weeks of limited weight bearing (20kg) was allowed. With this rehabilitation protocol, and stable internal fixation it seems that solid bone healing is achieved regardless of bone grafting material.

Biomechanical study

In the cyclic loading study, it was possible to judge the accumulation of damage (plastic deformation). ICPC stabilized the construct thus preventing it from further displacement during cyclic loading, whereas the group without ICPC showed a continuous drift displacement. Still some irreversible unloaded displacement was found in the ICPC group. Thus, probably some compaction of the bone tissue occurred before the cement showed the full stabilizing effect, which also could be the reason why the stiffness increased in both groups during the 100 cycles. This was probably due to the impaction of the bone-implant interface in both the control group and the ICPC group. Some impaction of the bone-cement interface probably occurred during loading in the ICPC group as the

cement was not injected under pressure. In our cyclic testing procedure, we mimicked loads comparable to normal gait, and found that calcium phosphate cement minimized the amplitude of the axial micromotion during cyclic loading.

In the load-to-failure study on composite tibias the ICPC-group was both stiffer and failed at larger loads than the control group. Still the failure load found in the control group was sufficient to withstand loads expected during normal gait, and the found maximal stiffness in the control group would result in amplitudes between 0.5 and 1mm during walking if translated into a normal walking cycle. Ideally, early weight bearing would induce the optimal amount of micro movement securing healing and accelerating rehabilitation. This has been investigated by several groups (100-102). Claes et al. made a transverse osteotomy on the metatarsus of goats. With osteotomy-lengths of 1mm, 2mm, and 6mm, the healing of the osteotomy was assessed after low and high interfragmentary stress. It was found that high grades of stress stimulated the healing in the small osteotomies while it delayed the healing in the larger osteotomies (100). Augat et al. showed in a similar model on goat tibia that transverse movement in the osteotomy delayed healing as opposed to axial movement which stimulated the healing (102).

It would also have been interesting to investigate the influence of torsion forces since ICPC's displays some weaknesses when exposed to torsion (72). However, axial loading is still the major force acting on the knee, and we found it more important to test the construct regarding failure-load and cyclic loading.

One should be precautious to apply the current biomechanical results to clinical practice: The donors of cadaver tibias were older than the typicall osteotomy candidate, thus the tested specimens probably were weaker, thus the displacement found is probably higher than they would have been if specimen had been 10 years "younger" (103). Having some biomechanical features in common with human tibias, the internal architecture of the composite tibias however is different with a much denser "trabecular bone". This denser trabecular bone is potentially introducing a bias, as the denser "trabeculae" provides more support for the ICPC than human tibial trabecular bone would have done, perhaps augmenting the measured effect of ICPC on load-to-failure. However, it can not explain the great differences found, since the measured effect of ICPC was also massive in the cadaver tibias with their more fragile trabeculae.

Randomized clinical RSA-study

The main purpose of the clinical study was to evaluate the stability of the open-wedge osteotomy construct, as measured with RSA, with three different bone graft materials: Local bone autograft, iliac crest bone autograft and the injectable calcium phosphate cement Calcibon. The study was designed to reveal a difference of 1 mm in MTPM after one year which we considered to be a clinically significant change in osteotomy movement. We did not find such clinically relevant difference as the biggest difference was 0.8 mm. We found only minor migrations regardless of bone grafting material. All three groups migrated the largest part during the first three months where Calcibon stabilized the osteotomy the most, but not statistically significant.

After one year the hardware was removed and loaded RSA were performed allowing inducible displacement to be calculated. This revealed that the osteotomies generally were stable without supporting osteosynthesis, apart from one patient that had been evacuated due to suspected deep infection.

In the biomechanical study we found that ICPC stabilized the osteotomy under loading mimicking normal walking. But we did also find that the implant itself seemed to be stable enough to withstand the loadings found during walking (I). This might be the reason why the migration in the two autograft bone groups also was small in the present study. Another explanation could be the biological reaction to Calcibon i.e. a mixed soft tissue response with fibrous covering of the Calcibon surface (II). This might influence the stability of the osteotomy.

Clinically improvements were seen in all subscores at the two year control. Surprisingly, the Calcibon group displayed the lowest scores at almost all timepoints in all subscores, especially knee related symptoms and quality of life, in spite of the lower migration. This could also be explained with the mixed soft tissue response (II).

Some limitations to the current study should be noted. In theory, the influence of eventual confounders is minimized in a randomized study as the current. Eventual confounders as smoking and weight were evenly distributed between groups. But the power of the study would have improved with a larger study population. The size of the study population was unfortunately diminished, and dropouts were unevenly distributed as more patients dropped out in the iliac crest bone autograft group. Stability is only a surrogate parameter to evaluate the healing. But it is well known that stability is of major importance for the bony healing and that delayed healing can lead to loss of correction, i.e. recurrence of varus malalignment. RSA is generally accepted as the

method to determine eventual migration and our results are in concordance with the findings by Magyar et al. (84).

All patients in the present study were operated and rehabilitated according to same protocol.

Differences in migration and clinically outcome therefore can be attributed to the choice of graft type.

Histological gap healing

The local biomechanical environment could be the reason why more than half the ICPC specimens had more than 50 % covering of the cement surface with fibrous tissue. In the biomechanical study we found amplitudes of approximately 0.7 mm when ICPC was used as void filler (I). According to Claes et al. this is probably approaching the limit for a healthy bone healing environment. So, one might speculate that the filling of the gap with ICPC, results in small but mechanically fragile interfaces, with relative pronounced strain, inhibiting cement resorbtion and bone apposition (100). We did observe fibrous tissue reaction, at the bone-ICPC interface, which might be the result of harmful amplitudes resulting from weight bearing during the preceding period of time. But in the bone groups only minimal fibrous tissue was present, in spite of being exposed to approximately the same loading pattern.

In our study, graft healing was evaluated, in core biopsies from the central part of the osteotomy, at one year postoperatively by quantitative histomorphometric analysis. In the two bone autograft groups no statistically significant differences was found, when comparing bone volume fraction and trabecular thickness. This was the case both in the adjacent bone and in the defect. The adjacent bone was found to be similar in all three groups, and comparable with the bone structure in the defects.

In previous experimental studies ICPC was remodeled, although slowly to bone tissue without soft tissue reaction i.e. there was no fibrous tissue as opposed to our findings (24-26). In experimental and clinical studies of fractures of the lateral tibial condyle, augmentation with injectable calcium phosphate cement gave comparable or better initial stability securing better final reduction, when compared to bone auto- or allograft. Histological, slow remodeling was found (27;74-76).

All of the biopsies were acquired at the same time point, after plate removal, one year postoperatively. To investigate the degree of new bone formation during the healing process at defined time intervals we could have used fluorochrome labeling with tetracycline and/or acquired serial biopsies. Due to ethical considerations this approach was not included in the study. To

minimize trauma and risk of weakening the healed osteotomy, the biopsies were obtained from the central part of the osteotomy where both the bone density, and probably also the loading, is lower than at the periphery. Bone remodeling might progress more slowly in the central part of the osteotomy, and it is likely that we would have found a more active and "healthy" bone-cement interface in the periphery due to beneficial mechanical stimulation.

The core biopsies were harvested with a 6mm trephine, through the most proximal of the distal screw-holes. This method secured some standardization and minimizing trauma to the patient, but also diminished control with the harvesting conditions of the biopsy increasing the risk of damage to the biopsy. The optimal, but clinically unethical, alternatives could be to remove a full thickness block from tibia, or perhaps a medial block potentially weakening the healed neocortex. Trabecular thickness was measured to overcome the obstacles of eventual compressive damage during harvest, since the trabecular thickness would be unaffected of eventual compression.

It might have been interesting to investigate the 3-D architecture of the osteotomy (104).

Conclusion

The studies included in the present thesis investigated the influence of different bone grafting materials on stability, bone healing and clinical outcome of OW-HTO stabilized with a titanium plate and non-locking screws.

In the biomechanical study (study I) we found that injectable calcium phosphate cement (ICPC) improved the primary stability of the osteotomy construct regarding cyclic displacement under loading conditions mimicking normal gait (hypothesis 1), and increased the load-to-failure (hypothesis 2).

In the randomized clinical study (Study II) we could not prove our hypothesis that ICPC, in the clinical setting stabilizes the osteotomy as measured with RSA, when compared to iliac crest bone autograft and local bone autograft (hypothesis 3). Osteotomies grafted with ICPC displayed less, but non significant migration than the bone autograft groups. Clinically, the ICPC group had worse outcome than the other groups, especially at the end of the study period, thus disproving that the stabilizing effect of ICPC also would result in better clinical outcome (hypothesis 4).

In the same randomized study, core biopsies were harvested at hardware removal after one year (study III). As evident on radiographs, the biopsies revealed large amounts of ICPC present in the osteotomy gap, inducing a mixed soft tissue response, including fibrous tissue covering of the cement surfaces, disproving ICPC to be osteoconductive and resorbable when used as bone substitute in OW-HTO (hypothesis 5). Grafting with local or iliac crest bone autograft resulted in uniform healing of the osteotomy gap regarding bone volume fractions and trabecular thickness (hypothesis 6).

To sum up the conclusions, we found that ICPC stabilized the construct in vitro and to some extent in vivo. Clinically ICPC seemed to perform less well than the other groups especially at the end of the follow-up period. It is concerning that ICPC only remodels slowly, and induces a varying soft tissue response, as opposed to grafting with bone autograft which seems to heal safely.

Suggestions for future research

The studies suggest that with a titanium implant and non-locking screws no further grafting is necessary. Thus it is a question if further clinical achievements can be accomplished with other bone grafting materials or factors affecting bone healing and metabolism e.g. demineralized bone matrix, bone morphogenic proteins, stem cells, bisphosponates, D-vitamin or parathyroid hormone.

More importantly, the biomechanical study suggests that immediate full weight bearing can be allowed. Full immediate weight bearing would provide a major improvement in rehabilitation and needs to be studied.

Another problem which not has been addressed in the present studies is to optimize proper selection of the ideal osteotomy candidate, and further whether and when conservative treatment or arthroplasty should be considered.

Large randomized clinical trials are needed to solve these problems.

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You tried your best and you failed miserably. The lesson is, never try

Homer Simpson

An expert is a person who has made all the mistakes that can be made in a very narrow field.

Niels Bohr (1885 - 1962)

Appendix: Studies in full text

I. Calcium phosphate cement enhances primary stability of open-wedge high tibial osteotomies. Two biomechanical studies in cadaveric and composite tibias.
Thomas Lind-Hansen, Poul Torben Nielsen, Juozas Petruskevicius, Benny Endelt, Karl Brian Nielsen, Ivan Hvid, Martin Lind.
Submitted

II. Open-wedge High Tibial Osteotomy. A randomized study of three different bone grafting materials with two years follow-up. Roentgenstereometric analysis and clinical outcome.
Thomas Lind-Hansen, Martin Lind, Poul Torben Nielsen.
Manuscript

III. Open-wedge osteotomy. Histomorphometric evaluation of three bone graft materials. A randomized controlled study.
Thomas Lind-Hansen, Martin Lind, Poul Torben Nielsen.
Manuscript

Paper I

Calcium phosphate cement enhances primary stability of open-wedge high tibial osteotomies
Two biomechanical studies in cadaveric and composite tibias

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ABSTRACT

INTRODUCTION

We investigated if injectable calcium phosphate cement (ICPC) improves primary stability in open wedge high tibial osteotomy.

MATERIALS AND METHODS

A 10-mm open-wedge osteotomy was performed on eight pairs of preserved cadaver tibiae and seven pairs of composite (Sawbone®) left tibiae. Osteosynthesis was performed with the Dynafix plate ® system. The gap resulting from surgery was filled with either 15g of ICPC in half the bones, or left untreated. The composite tibiae were loaded at a ramp speed of 20mm/min up to 20kN. The cadaver tibiae were exposed to 100 cycles with a maximum compressive force of 2250N.

RESULTS

Final loaded displacement after 100 cycles of loading with 2250 N was 1.2mm for the cadaver tibiae treated with ICPC compared with 3.6mm for the empty defects ($p = 0.028$). All seven empty defect composite specimens failed before 20kN (median 2.8kN), compared with five of the ICPC specimens (median 17kN) ($p = 0.005$).

CONCLUSION

Injection of ICPC after open-wedge osteotomy of the proximal tibia increases the initial stability of the bone as measured by load-to-failure and displacement after cyclic loading. Clinical studies are ongoing to investigate whether ICPC also has clinical advantage on wedge healing and stability.

Key words

Tibial osteotomy, bone graft materials, biomechanics, osteoarthritis

BACKGROUND

Osteoarthrosis (OA) of the knee is a potentially disabling disease in young patients who are not suitable for total knee replacement treatment. Therefore, optimal treatment regimens are needed for all stages of knee osteoarthrosis. Treatment of the young and active patient with early stages of unicompartmental osteoarthritis still remains a challenge. Different surgical options include Total Knee Replacement, Unicompartmental Knee Replacement, and High Tibial Osteotomy (HTO) (1;2).

In recent years, open-wedge HTO has gained popularity in the treatment of medial knee osteoarthritis with a varus malalignment. The methods used are either distraction by hemicallostasis with external fixation or internal fixation (3-6). The latter, however, leaves a gap with a medial opening of up to 2cm. To secure healing of the osteotomy, different bone graft materials are suggested by various authors. Autograft is considered the gold standard as it secures healing (3;5;7-9) but also includes disadvantages, i.e. limited availability and donor-site morbidity (10). Another alternative is allograft which entails a minor risk of virus transfer (11).

Several bone substitutes have been introduced for gap healing in open-wedge HTO, either alone or in combination with autograft or allograft: Hydroxyappatite (HA), Beta Tricalcium Phosphate, and acrylic cement (3;8;9;12-14).

With or without grafting, delayed healing is reported in up to10 % of operations performed (3-5;7-9;12-14). Delayed healing and non-union are associated with implant failure and loss of correction resulting in inferior results. With optimal bone grafting material and postoperative rehabilitation regimens these problems could be avoided. As bone grafting material injectable calcium phosphate cement (ICPC) could be beneficial, as it offers osteoconduction and initial high compressive strength(15-18) and thereby, in theory, enhances the primary stability.

The aim of the present study was to investigate if calcium phosphate cement, as supplement to internal fixation, improves the primary stability of the open-wedge osteotomy construct and thereby potentially allows early weight bearing.

We hypothesized that ICPC improves the primary stability of the open wedge osteotomy construct, resulting in minimized displacement after axial cyclic loading, as found during walking, and higher load-to-failure after axial loading.

MATERIAL AND METHODS

Study design

Two biomechanical studies were conducted.
In both studies specimens were randomly assigned to either ICPC or empty gap. All specimens had the same osteosynthesis of the osteotomy.
Study one: eight pairs of cadaveric tibias (left and right) were tested to investigate displacement after cyclic, axial loading. DEXA scan was carried out before the operation for comparison of bone mineral density (BMD).
Study two: seven pairs of composite tibias (left/left) were tested to investigate axial load to failure. It was calculated that minimum seven specimens should be included in both groups (see statistics).

Materials

ICPC

We used Calcibon® (Biomet Merck GmbH) which is a synthetic, biodegradable, calcium phosphate based bone substitute. It is intended for filling of metaphyseal, cancellous bone defects. The material is mixed during the operation from a liquid consisting of an aqueous solution of disodium hydrogen phosphate (2.5% NaHPO4) and a powder part consisting of 58% α-TCP (Tri Calcium Phosphate), 8.5% PHA (Precipitated Hydroxyappatite), 25% CaHPO4 (Calcium Phosphate), and 8.5% CaCO3 (Calcium Carbonate). The resulting paste is applied directly and hardens at body temperature. The chemical composition and crystalline structure of the cured material mimic the mineral part of natural bone.
The compressive strength of the material increases during the hardening process. After six hours it is comparable to cancellous bone. The final compressive strength is reached after three days and is up to 60MPa (16;17;19).

Cadaveric bones

The cadaveric bones were pairs of tibias supplied by the program of “Body Donation to Medical Science, Institute of Anatomy, University of Aarhus”. The bones were preserved in glycerine, formalin, and 96% alcohol. The specimens were stripped of skin and muscles, and fibula was removed. All specimens had periosteum and pes anserinus in place.

Composite bones

The composite bones were fourth generation composite tibia (Sawbones®, Pacific Research Laboratories, Inc., Vashon, USA) which have been validated for biomechanical testing (20).

Methods

DEXA scan of cadaver specimens

Measurements were performed with the Norland XR-36 Bone Densitometer (dual-energy X-ray absorptiometer) under standardized conditions in a customized fixture securing uniform orientation. The scans were performed in the “research” mode with a resolution of 1×1mm and at a speed of 60mm/s. Calibration was performed daily with two different phantoms according to the guidelines

of the manufacturer. For the BMD analysis, a 2x2cm ROI was defined centrally in the subchondral region, 2cm below the tibia eminence (Fig. 1).

Osteotomy and osteosynthesis

On the cadaveric bones a standard vertical incision over the proximal medial aspect of tibia was used. Pes anserinus was deflected posteriorly to allow proper plate-bone contact. An oblique infracondylar, subperiosteal osteotomy was then performed with a saw and osteotome. To secure that a standardized osteotomy was performed on the composite bones, a custom moulded cast was used for each specimen.
In both studies we performed a medial, 10-mm open-wedge osteotomy. Opening of the osteotomy was performed with the bone spreader provided in the Dynafix® VS™ Osteotomy System (Biomet Merck GmbH). We have excluded specimens if a fracture of the lateral bony hinge was observed, macroscopically or on intraoperative fluoroscopy, during opening of the osteotomy. Osteosynthesis was performed with the Dynafix® VS™ Osteotomy System. The plate was fixed with 6.0mm screws. Proximal screws were placed subchondrally and uni-cortically. Distal screws were bi-cortical. The osteotomy-gap was filled with 15g of ICPC in half the bones, whereas the other half were left untreated **(Figure 2a-d).** The handling directions of manufacturer were followed. Assignment of a specimen to either ICPC or control was chosen by random numbers. All bones were kept in a moisturized (isotonic saline) cloth at 37° in an attempt to mimic physiological conditions and secure evenly curing of the cement paste**.**

Mechanical Test set-up

We chose a mechanical axis transecting at the 62%-point of the medio-lateral diameter of the proximal tibial plateau, as this is the axis we usually strive to achieve, aproximating 3º-5º of valgus (21;22). The proximal tibial joint surface was prepared for cement-fixation by drilling three anchorage holes (6mm diameter) and then rigidly fixed in polymethylacrylat (Refobacin® Bone Cement R). Correct orientation exactly on the planned mechanical axis was secured by centralizing the distal and proximal points of passing of the mechanical axis in a clamp during cementation. After curing of the cement on the proximal end, the specimens were shortened leaving the proximal 13.5cm. Finally the distal part was potted in bone cement, and the specimens were ready for test **(Figure 3a-e).**

Test-procedure

The specimens were tested in an Instron Universal Material Testing Machine (Model 5568, Serial No. H1504, Instron®, UK) (Fig. 3b). The load cell was an Instron Load Cell, Type 2525-8002, Serial No UK044, with an accuracy found to be equal or better than 0-1% of cell rated output or 0-5% of indicated load, whichever is the greatest.

Study 1, cadaver bones, displacement after cyclic test

Starting with a maximal load of 200N for ten cycles, increasing maximal loads were applied at 750N and 1500N for each ten cycles. Then 100 cycles with a maximal load of 2250N were performed. The 2250N corresponds to the load on the knee at normal walking for a person of 75kg (3 x the person's weight (23)).
Test parameters:

- Unloaded displacement at the start of the first and last full cycle with 2250N
- Loaded displacement at the conclusion of the first and last full cycle with 2250N

- Stiffness of the construct in the first and last full cycle with 2250N
- Amplitude of the first and last full cycle with 2250N

Study 2, composite bones, load-to-failure test

The specimens were loaded at a ramp speed of 20mm/min until a maximal load of 20kN. Data were recorded every 10N. Failure was defined as the point at which the first reduction in loading occurred (24).
Test parameters:

- Failure load, defined as the first peak on the load-displacement curve
- Stiffness, defined as the maximum slope of the load-displacement curve before failure
- Energy absorption, defined as the area under the load-displacement curve before failure

Data were recorded on a pc as data points with corresponding loads (Newton) and displacement (mm). Calculation and identification of the parameters were auto generated in SPSS.

Statistics

Means and standard deviations were calculated. Load-to-failure was also compared with Cox regression. Data were found to be normally distributed. Differences were tested with paired t-test and Students t-test. A p-value below 0.05 was considered significant.
The study was designed to find an increase in load to failure, and decrease in displacement of 25% with expected standard deviation of 15% and a risk of type 1 error of 5% and a power of 80%. To find such a difference, seven specimens were needed in each group.

RESULTS

Study 1, Cadaver bones, displacement after cyclic test (table 1, figure 4)

Mean age of the donors were 73 years and 8 month. Preoperative BMD measurements of the proximal part of the tibia were performed to test for intra-individual side-to-side variability in the bone mineral density (BMD: control-group = 0.41g/cm² (95% CI, 0.3-0.5), ICPC-group = 0.36g/cm² (95% CI, 0.30-0.41), P-value = 0.19, paired t-test).
After the initial "preconditioning" cycles, displacement did not "return" to zero at relaxation. There was no significant difference in unloaded displacement between the two groups after the preconditioning cycles. In the ICPC-group stiffness was more than four times higher ($p < 0.001$) than the empty gap-group, and the loaded displacement at completion of first full cycle in the empty gap-group was nearly twice the size of the ICPC-group ($p = 0.006$). After the 100 cycles with 2250N, ICPC showed a stabilizing effect on the construct with significantly higher stiffness and lower loaded and unloaded displacement values than the control group. The amplitudes were significantly larger in the control group with amplitudes of 1.3 (first cycle) and 1.5mm (last cycle) compared with consistent amplitudes of approximately 0.7mm in the ICPC-group. The amplitudes did not change significantly throughout the 100 cycles in both groups.

Study 2: Composite bones, load-to-failure (table 2, figure 5)

Failure occurred before 20kN in all of the control specimens (mean 4.2, median 2.8kN), but only in five of the ICPC specimens (mean 15, median 17KN). As two of the ICPC specimens did not fail,

survival analysis vas also carried out. Cox-regression revealed a significant difference in survival until load-to-failure with a Hazard Ratio of 0.1 ($p = 0.005$).
Maximum stiffness also showed significant differences between groups as did the energy absorption. Still the failure-load noted in the control group exceeded the load expected to be encountered during normal walking of a 75kg person (approximately three times body weight).

DISCUSSION

To our knowledge this study is the first biomechanical study to test the biomechanical properties of a synthetic bone substitute used in HTO.
We have demonstrated that the injectable calcium phosphate cement Calcibon®, as a supplement to internal fixation, stabilized the HTO construct in cyclic axial loading and axial load-to-failure in cadaver- and composite tibia-models, respectively.
In the cyclic loading study, it was possible to judge the accumulation of damage (plastic deformation). ICPC stabilized the construct thus preventing it from further displacement during cyclic loading, whereas the series without ICPC showed a continuous drift of the total displacement, indicating a steady growth in the displacement for cyclic loading. Still some irreversible unloaded displacement was found in the ICPC group. Thus, probably some compaction of the bone tissue had to occur before the cement showed the full stabilizing effect.

Interestingly, the stiffness increased in both groups during the 100 cycles. This was probably due to the impaction of the bone-implant interface in both the control group and the ICPC group. Some impaction of the bone-cement interface could probably occur in the ICPC group as the cement was not injected under pressure. In our cyclic testing procedure, we mimicked loads comparable to normal gait, and found that calcium phosphate cement minimised the amplitude of the axial micromotion during cyclic loading.

In the load-to-failure study on composite tibias the ICPC-group was both stiffer and failed at larger loads than the control group. Still the failure load found in the control group was sufficient to withstand loads expected during normal gait, and the found maximal stiffness in the control group would result in amplitudes between 0.5 and 1mm during walking if translated into a normal walking cycle. Ideally, early weight bearing would induce the optimal amount of micro movement securing healing and accelerating rehabilitation. This has been investigated by several groups (25-27). Claes et al. made a transverse osteotomy on the metatarsus of goats. With osteotomiy-lengths of 1, 2, 6mm, the healing of the osteotomy was assessed after low and high interfragmentary stress. It was found that high grades of stress stimulated the healing in the small osteotomies while it delayed the healing in the larger osteotomies (25). Augat et al. showed in a similar model on goat tibia that transverse movement in the osteotomy delayed healing as opposed to axial movement which stimulated the healing (27).

Previous studies have tested the stability of devices for internal fixation most often used in HTO (24;28-33). Stuart (28) investigated the first generation of the Puddu Plate® (Artrex, Naples, Fla) on frozen cadaver tibias and found it only marginally stable to withstand axial loading and marginally insufficient to withstand torsional loadings during gait. Since then, the Puddu Plate has been modified. In studies on different implants for internal fixation, load to failure was found to be in the range of 1.6kN-2.9kN. Highest failure loads were found for long rigid plates with interlocking screws (31). Stiffness was found to be in the range of 1349N/mm – 2425N/mm, highest for a short spacer plate (31;32). Miller et al. investigated the stability of open-wedge osteotomies performed on Sawbones® using the Dynafix® VS™ Osteotomy System which was the osteotomy system tested in this study. They found that the stiffness of the construct was 2425 +/- 418N/mm in axial loading with an intact bony lateral hinge. After breakage of the lateral hinge, the stiffness was reduced to 1030 +/- 322N/mm (31).

In open-wedge HTO different bone grafting materials are used to fill the osteotomy-gap. Autograft, mainly from the iliac crest, is considered gold standard (3;5;7;8), but shortcomings include limited availability and donor site morbidity, as 30-40% of the patients report complaints of pain at the donor site, six month after operation (10). Allograft does not induce donor-site morbidity, but carries a minor risk of transfer of infectious agents. Therefore synthetic bone substitutes have been introduced. Synthetic bone substitutes should ideally be biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use, and cost-effective (11).

Several authors have investigated the healing response of different graft materials in open wedge osteotomies. Hernigou used a full bony wedge from the iliaca crest in the osteotomy gap without internal fixation. He observed 11/93 with loss of correction due to fracture of the lateral cortex. With the introduction of internal fixation, no collapses were observed (5).

In 50 operations, with full thickness iliac crest grafts, Devgan reported no non-unions, but one case of collapse of the bony graft, resulting in loss of correction (7). Without further specifications, Lobenhoffer used “local cancellous bonegraft” in minor corrections (<10°) and wedges from either iliac crest or hydroxyappatite/tricalciumphospate in larger corrections. In 101 operations with the Arthrex® osteosynthesis there were six cases of non-union and associated implant-failure. After technical modifications, including changing of osteosynthesis to a plate fixator with locked bolts (TomoFix™), no further cases of non-union were noted (3). Koshino found no cases of collapse after ten years, in 21 cases treated with open-wedge HTO with a combination of hydroxyappatite-wedges and autologous fibular bonegraft (9). Staubli et al. (14) did not use bone substitutes and argued that the osteosynthesis fixation devices yielded sufficient stability. In 92 operations they reported two cases of delayed union and loss of correction after removal of osteosynthesis material before 12 month. One study reports on clinical results with cement usage. Hernigou filled the osteotomy gap with acrylic cement and reported two delayed healings, one non-union out of 245, and no problems with succeeding TKR (12).

In our study we investigated the stabilizing effect of ICPC used as bone graft material in the ostetomy opening in vitro. We did not test the use of bone autograft or allograft because it does not yield initial mechanical support as described by Spahn and Wittig (29). In contrast, injectable and remodelable calcium phosphate cements offer supplementary stabilization to osteosynthesis. Frankenburg investigated ICPC Norian®, also an ICPC, in a metaphyseal defect on canine tibia and femur. Biomechanical evaluation shoved compressive strength superior to normal bone and after eight weeks, the torsional strength was almost that of the intact tibia. Histological evaluation showed slow remodeling – after 32 and 72 weeks, the architecture of the bone was only approaching that of normal bone (15). Ooms studied Calcibon® in the same manner in diaphyseal defects. He found intimate bone-cement contact, without any fibrous tissue. He also observed slow remodeling, with most of the cement in situ after 24 weeks (16;17). In experimental and clinical studies of fractures of the lateral tibial condyle, augmentation with injectable calcium phosphate cement gave comparable or better initial stability securing better final reduction, when compared with bone autograft or allograft. Histologically slow remodeling was found (18;34-36).

This study has evaluated the primary stability of the open wedge construct with and without ICPC. We mimicked the clinical setting by using the same operative technique and fixation devices as in standard surgical settings. Also we aligned the specimens so the mechanical axis passed through the desired points. Preoperative DEXA-scan of the proximal part of the tibia was performed, demonstrating low intra-individual side-to-side variability in bone mineral density. However, the

average age of the cadaver specimens was 73 years, which is approximately a decade older than the typical open wedge osteotomy candidates. The tibias used in the present study are therefore probably weaker than would be expected in clinical practice. The composite tibias have been manufactured to possess the same biomechanical properties as human bones under axial bending. As they have a low inter specimen variability, they were regarded suitable for axial biomechanical testing (20). In our test set-up, all specimens were shortened thereby loosing some of the elasticity of the long bone resulting in a more direct transmission of the axial load. We could not control the penetration of the cement as the injection of ICPC was performed without pressurizing, as it is usually done in clinical practice. However, the lack of circulation in the specimen in the present study differs from patients where cement penetration maybe smaller due to bleeding. But as we study relative differences we mean that the differences found in our study also apply in vivo. Our study suggests a beneficial initial mechanical effect of ICPC when used in open-wedge tibial osteotomies. However, possible clinical advantages of these results, regarding possible early weight bearing and reduced non-union rates, still need to be investigated in a clinical study.

CONCLUSION

The injectable calcium phosphate cement Calcibon® minimizes the displacement and amplitudes during cyclic testing and enhances primary stability during load to failure in open wedge osteotomies on the proximal tibia. The clinical implications of our study could be early weight bearing and faster rehabilitation after open-wedge osteotomy. Clinical studies are needed to support these findings and to investigate the biologic response to ICPC. We await our ongoing randomized controlled trials on this subject.

Acknowledgements - Disclosures

The authors wish to thank: The Program of Body Donation to Medical Science, Institute of Anatomy, Aarhus University. The study was financially supported by the following non-commercial institutions: WSF – Western Denmark Health Research grant of Aarhus University, Danish Rheumatism Association, The Opel Family Foundation, The Spar Nord Foundation. The study have benefited from institutional research support from the following company with commercial interests in this research area: Biomet Denmark

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Figure legends

Fig. 1

DEXA-scan of proximal tibia marked with 2x2cm ROI centrally in the subchondral region, 2cm below the tibia eminence.

Fig. 2

A standardized osteotomy was made with a saw in a custom made moulded cast (a, b). The osteotomy was carefully opened and stabilized with osteosynthesis (c) and filled with 15g of Calcibon® (d).

Fig. 3

Exact alignment of the mechanical axis was secured before potting the proximal end, while maintaining the correct axis (a). After curing of the cement, the shortened specimens were ready for the tests (b).

Fig. 4

Results study 1, displacement after cyclic loading, cadaver bones. Each line showing displacement at the observation points for each specimen in the two groups.

Fig. 5

Results study 2, Load-to-failure, composite bones. Curve showing failure-load for the two groups.

Table 1, Study 1, cadaver bones - Displacement and stiffness after cyclic loading

	Control (N = 8)		Calcibon (N = 8)				
	Mean	**SD**	**Mean**	**SD**	**Mean diff.**	**95 % CI**	**p-value**
Displacement (mm)							
Unloaded 1st cycle	0.70	0.31	0.46	0.19	0.24	-0.10 – 0.58	0.138
Loaded 1st cycle	1.98	0.55	1.12	0.18	0.86	0.33 – 1.40	0.006
Unloaded Last cycle	2.13	1.70	0.56	0.17	1.57	0.10 – 3.05	0.040
Loaded Last cycle	3.60	2.40	1.21	0.18	2.38	0.34 – 4.42	0.028
Stiffness (kN/mm)							
First cycle	3.1	0.7	14.7	5.3	11.6	7.2 -16.0	0.000
Last cycle	5.2	2.2	51.6	41.5	46.4	11.8 -81.1	0.016

Table 2, Study 2, Composite tibias, Load to failure

	Control (N = 7)		Calcibon (N = 8)				
	Mean	**SD**	**Mean**	**SD.**	**Mean diff.**	**95 % CI**	**p-value**
Load (kN)	4.2	3.4	15.1	5.1	10.9	5.9 – 15.9	0.000
Stifness (kN/mm)	4.8	0.9	11.6	1.4	6.8	5.5 – 8.1	0.000
Energy absorbtion (kN*mm)	3.8	6.0	24.3	22.0	20.5	1.9 – 39.0	0.035

Fig. 1

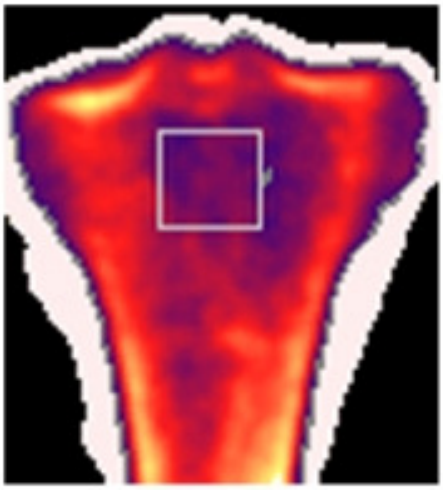


Fig. 2a

Fig. 2b

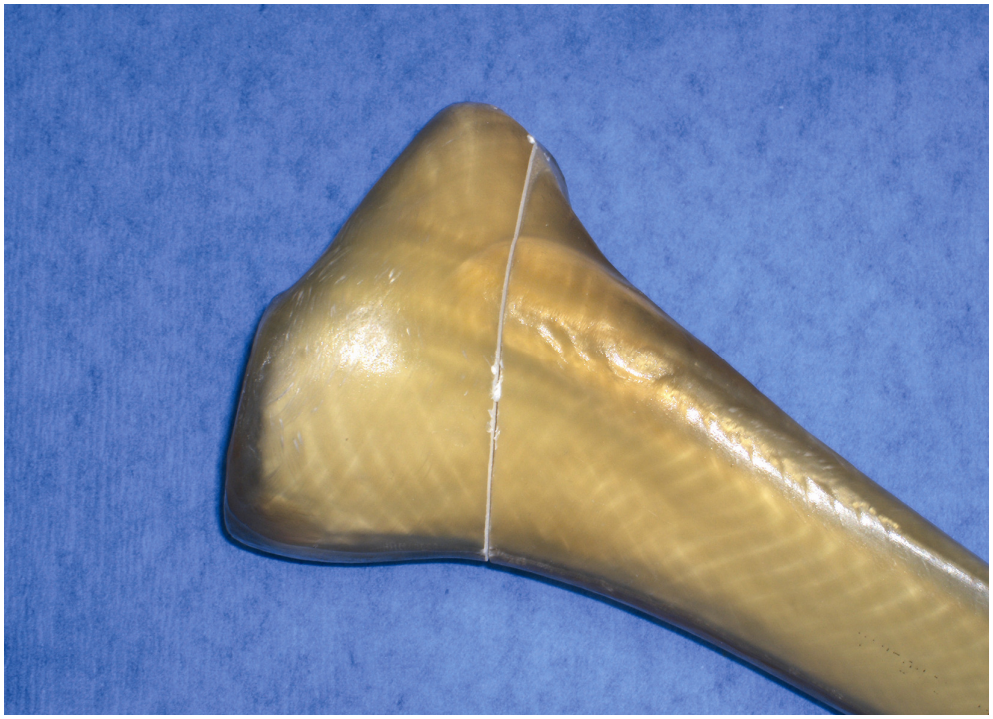


Fig. 2c

Fig. 2d

Fig. 3a

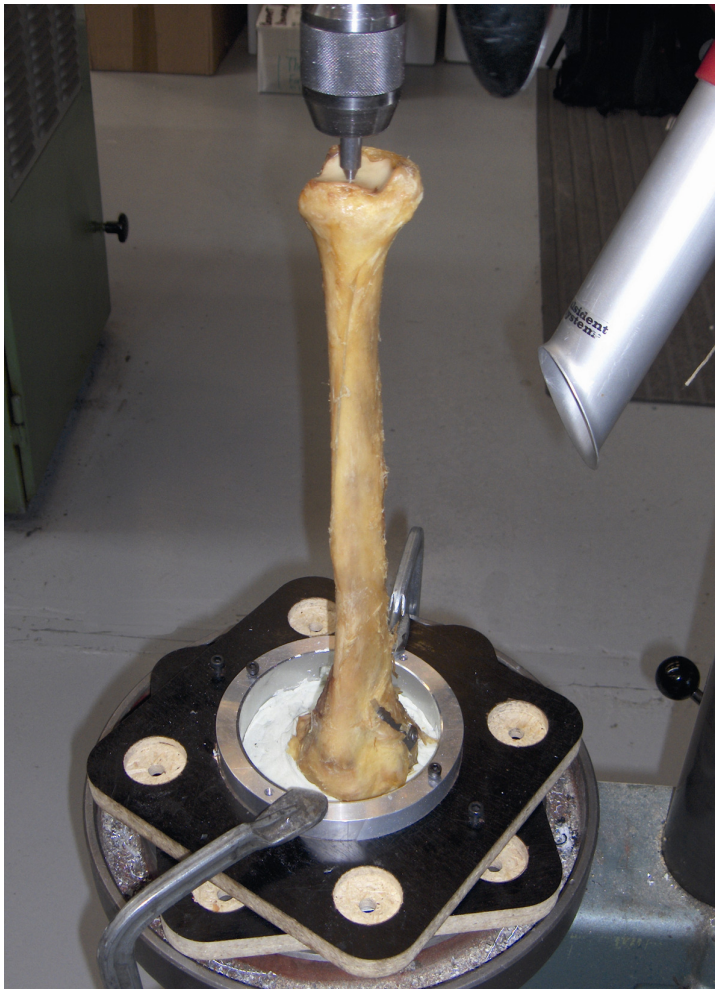


Fig. 3b

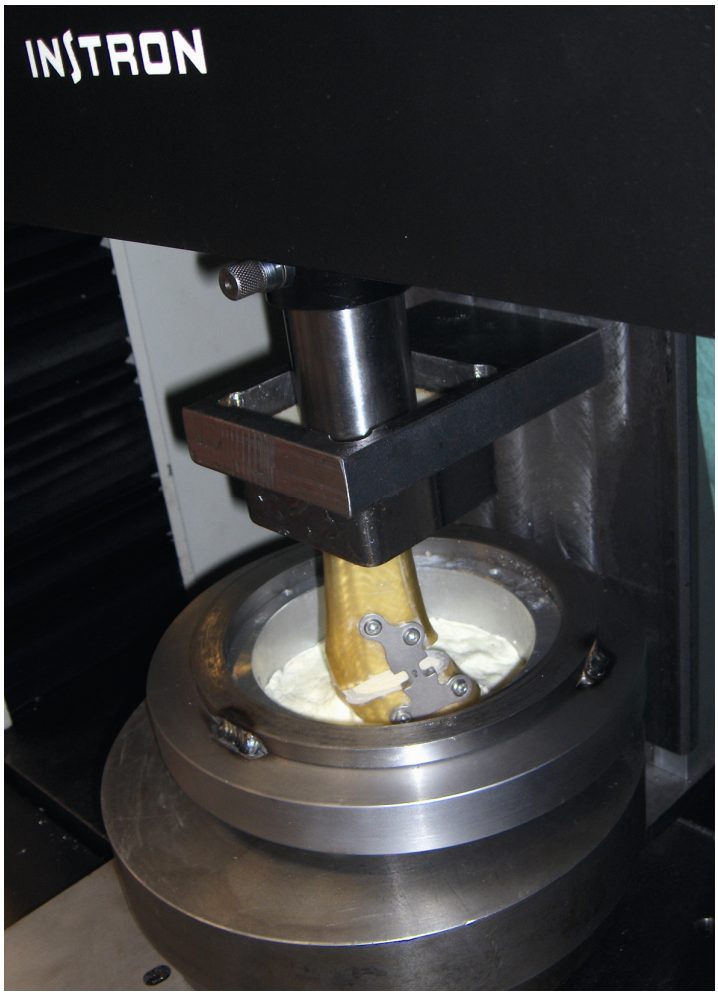


Fig. 4

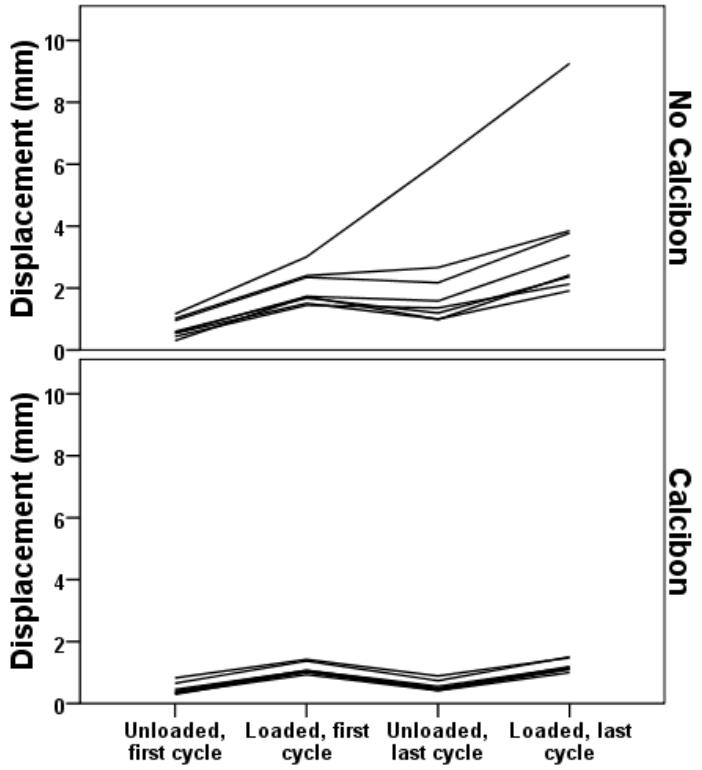
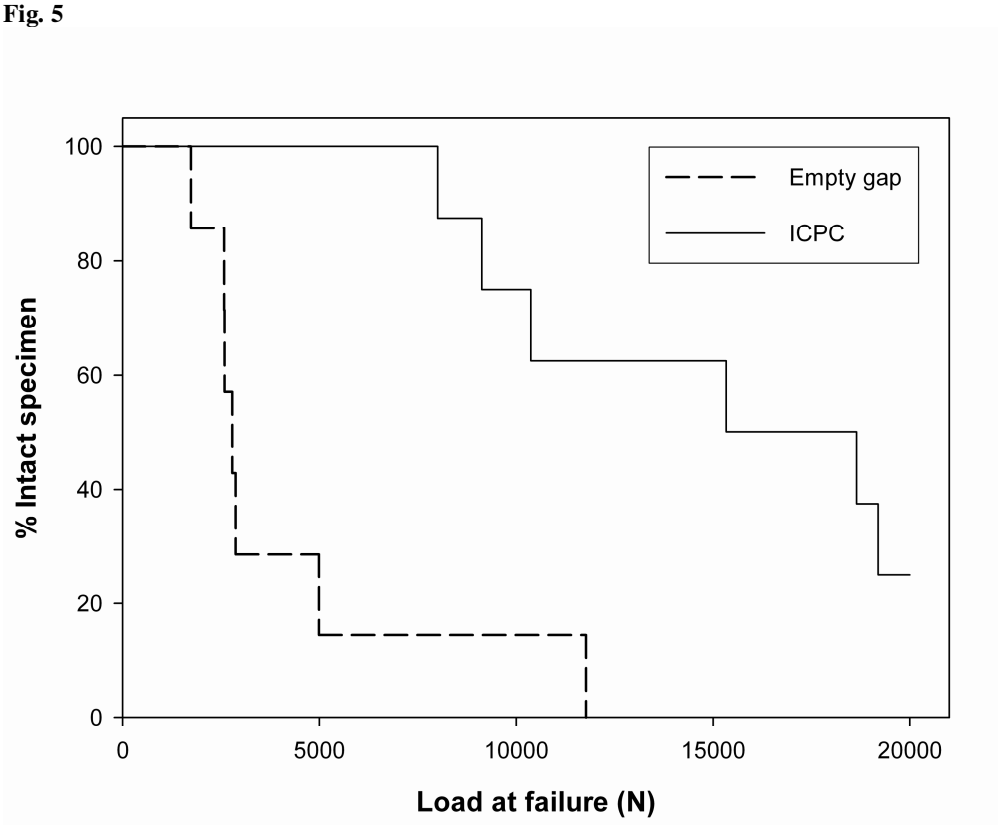

Displacement (mm)
No Calcibon
Displacement (mm)
Calcibon
0
2
4
6
8
10
Unloaded, first cycle
Loaded, first cycle
Unloaded, last cycle
Loaded, last cycle

Fig. 5


100
80
60
40
20
0
% Intact specimen
0
5000
10000
15000
20000
Load at failure (N)
Empty gap
ICPC

Paper II

Open-wedge High Tibial Osteotomy - A randomized study of three different bone grafting materials with two years follow-up – roentgenstereometric analysis and clinical outcome

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Abstract

BACKGROUND

Open-wedge high tibial osteotomy (OW-HTO) is a well established treatment for the young and active patient with unicompartmental knee OA. Consolidation of the bone defect is mandatory to maintain the obtained axial correction. The influence of different bone grafting materials on stability and healing OW-HTO is unknown.

MATERIALS AND METHODS

45 (3x15) patients, were randomized to 3 different bone grafting materials: local autograft, iliac crest autograft, injectable calcium phosphate cement (Calcibon®). Stability of the healing osteotomy was evaluated with radiostereometric analysis (RSA) postoperatively, and 3, 12 and 24 month postoperative. Furthermore clinical outcomes were evaluated with the knee injury and osteoarthritis outcome score (KOOS).

RESULTS

Translations and rotations close to zero were found regardless of bone grafting material. No statistically significant differences were found between the groups on either of the RSA-parameters at all time points. Clinically the Calcibon-group had lover quality of life KOOS subscore at two years follow-up.

CONCLUSION

In this randomized study, only minor difference in osteotomy stability over two years was found. We conclude that with a stable implant and six weeks of partial weight bearing, autografting is sufficient to achieve solid bone consolidation following OW-HTO.

KEY WORDS

Tibial Osteotomy, Bone graft materials, Histomorphometry Osteoarthritis

Background

Medial knee osteoarthritis with a varus malalignment can be treated successfully with an open-wedge high tibial osteotomy (OW-HTO). OW-HTO with immediate preoperative opening and internal fixationleaves a bone gap with a medial opening often exceeding 10 mm that can be left empty or filled with different bone graft materials as suggested by various authors (1-3). Autograft secures healing (1;3-6) but also includes disadvantages, i.e. limited availability and donor-site morbidity (7). Bone allograft is another alternative which entails a minor risk of virus transfer (8).
Several synthetic bone substitutes have been introduced for OW-HTO, either alone or in combination with auto- or allograft: Hydroxyappatite (HA), Beta Tricalcium Phosphate and acrylic cement. Still, only one randomized clinical study has been published. Dallari et al. found that platelet gel and the combination of platelet gel and bone marrow stromal cells increased the osteogenic potential of lyophilized bone chips after six weeks. However after 12 month all patients had complete clinical and function evidence of healing (1;5;6;9-12).
With or without grafting delayed healing is reported in up to10 % of operations performed. Delayed healing and non-union is associated with implant failure and loss of correction resulting in inferior results (1-6;9-11). In recent years better implants have improved the primary stability (13;14), but it is still unknown which bone graft materials should be used. As bone grafting material injectable calcium phosphate cement (ICPC) could be beneficial in OW-HTO, since it offers osteoconduction and initial high compressive strength (15-18). Recently, in a biomechanical study, we have shown that ICPC, as supplement to internal fixation, increases initial stability of the OW-HTO construct (own unpublished results, submitted).
The aim of the present clinical study was to investigate if different bone graft materials presented substantial benefits for the in vivo mechanical stability of the osteotomy and clinical outcome.
We hypothesized that the injectable calcium phospate cement Calcibon®, when compared to local bone autograft (trabecular bone chips released within the osteotomy gap) and iliac crest bone autograft, as supplement to internal fixation, improves the stability of the open-wedge osteotomy construct and facilitates the healing, resulting in minimal migration, as measured with RSA, and improved clinical outcome, as measured with knee injury and osteoarthritis outcome score KOOS.

MATERIAL AND METHODS

Study design

A randomized controlled trial was carried out with 45 patients who had an OW-HTO performed. After opening and ostetosynthesis of the osteotomy, sealed envelopes was opened in the operating theater, revealing the random assignment to either of the intervention groups:

4. Local cancellous autograft.
5. Iliac crest autograft.
6. Injectable calcium phosphate cement (Calcibon®)

The study was approved by the Ethics committee for the Viborg and Northern Jutland counties, Denmark, Study no.VN 2004/53, and registered at Clinical Trials Gov.

Patients

In the period 10th December 2004 to 12th June 2006 71 patients had a corrective open-wedge osteotomy (tibial or femoral) performed at our clinic. Of these, 61 were unilateral medial open-wedge osteotomies and met the inclusion criteria's (Table 1). 12 patients were excluded: 4 because of too high BMI, 3 because of intercurrent disease (necessitating further medical investigation and management at time of inclusion), and 5 rejected participation. 49 patients accepted to be included and signed informed content. Four were excluded after inclusion and signed informed consent but before operation: one had rapid progression of arthritis necessitating total knee replacement, one was operated at another clinic, one was excluded because of interim competing disease and one withdrew content to participation.
Thus 45 patients were randomized. See table 2 for patient characteristics.

Operating technique

Patients were operated in supine position using a tourniquet and fluoroscopy. Pes anserinus and periosteum was mobilized and deflected posterior to allow for the oblique infracondylar osteotomy. The osteotomy was initiated with saw and completed with osteotome. Opening of the osteotomy was performed with bone distractor and internal fixation was done with a titanium spacerplate and non locking 6.0 mm titanium screws (Dynafix® VS™ Osteotomy System (Biomet Merck GmbH)) (Fig.1).

Grafting procedures

1. Local bone autograft: Using a curette, the cancellous bone from the two adjacent cut surfaces was scooped out in the osteotomy defect creating a loosely woven bone network.
2. Iliac crest bone autograft: The height (h) and diameter (2*r) of the osteotomy, considering the gap a wedge, was used to estimate the gap volume ($V \sim \pi * r^2 * h/2$). Cancellous bone, corresponding to the volume of the osteotomy, was harvested from the iliac crest using the Accumed® Bone Graft Harvesting System (Acumed®, Oregon, USA). The system is minimally invasive enabling harvest of several milliliters of milled bone.
3. Calcibon®: The cement was mixed and injected into the osteotomy defect with a syringe. Enough paste was mixed to enable macroscopic filling of the osteotomy.

Injectable calcium phosphate cement

We used Calcibon® (Biomet Merck GmbH) a synthetic, biodegradable, calcium phosphate based bone substitute. The material is mixed from a liquid and a powder part. The powder part consist of 58 % α-TCP (Tri Calcium Phosphate), 8.5 % PHA (Precipitated Hydroxyappatite), 25 % CaHPO4 (Calcium Phosphate) and 8.5 % CaCO3 (Calcium Carbonate). The paste is injectable and can be applied directly and hardens after a few minutes. The chemical composition and crystalline structure of the cured material mimic the mineral part of natural bone. The compressive strength of the material increases during the hardening process. After 6 hours it is comparable to cancellous bone. The final compressive strength is reached after 3 days and is up to 60 MPa (16;17;19).

Roentgenstereometric analysis (RSA)

Basic principles

Roentgenstereometric analysis (RSA) is a highly accurate method of quantifying minute movements in the skeleton. It was introduced by Selvik (20) and has been used in open-wedge osteotomies, both in experimental (21) and clinical studies to determine micromotion (22;23).
The method is based on the principle that spherical tantalum markers project on the x-ray film which in combination with a calibration cage, defining a "laboratory coordinate system", enables calculation of 3-D coordinates of the markers. A minimum of three non-collinear spherical tantalum markers form a rigid body representing a segment, i.e. extremity, bone or prosthesis. Thus motion between two rigid bodies can be detected between two examinations.

Preparation for RSA

In the present study the first rigid body represented the articular bone segment above the osteotomy, and the second rigid body represented the distal bone segment below the ostetotomy (Fig. 2). Insertion of spherical tantalum markers was done after completion of osteosynthesis. In each segment we placed four to nine, 0.8 and/or 1.0 mm tantalum markers for ease of identification.

RSA examination

We used the bi-planar cage 10 (RSA Biomedical, Sweden) in combination with mobile x-ray tubes. Synchronous x-ray recordings were performed with patients leg aligned in the calibration cage in the same manner at each examination.

RSA images

Analog images where scanned in UmRSA Digital Scan on an Umax Power Look 2100 XL scanner. Spatial resolution where set to 300 DPI, scanning gamma correction (gray-scale) where set to 2.2 or 3.0 in dark images.
Digital images were transmitted and imported with use of the UmRSA DICOM Link with an image resolution of 254 DPI, in DICOM 3.0 format. UmRSA V. 6.0 software was used for measuring of images and calculation.

Rigid body configuration and stability

For accurate assessment of micromotion it is of paramount importance that the configuration of the rigid bodies is optimal and stable. This means that the tantalum markers should be well scattered (non-linear) in all three dimensions and stay in the same position. The degree of scattering is given

by the condition number (CN), where high numbers indicate poor scattering (24). The stability, of the tantalum markers constituting a rigid body, is given by the mean error of rigid body fitting (ME), representing eventual relative changes of the rigid body between two examinations – consequently a high ME implies a unstable rigid body. Following the guidelines given by Valstar et.al (25), we excluded examinations with CN above 150, and ME above 0.25.
Precision of the RSA-measurements at our laboratory is shown in table 2.

RSA parameters

The motion of the proximal articular segment was measured relative to the distal segment. Migration is reported as maximal total point motion (MTPM) and rotations around and translations along the 3 axes (X, Y, Z). MTPM represents the length of the translational vector of the marker that moved the most between two examinations. Several problems are associated with MTPM: It is very sensitive to loose markers, it is not necessarily the same marker that moved the most between different examinations, and the position of the measured marker is not the same from patient to patient making comparison incorrect.
To address these problems we therefore instead used the MTPM translational vector of fictive points representing the tibia eminences. This implies that easy identifiable (anatomical) landmark(s) is marked in one pair of images for each patient. The points are given 3-D coordinates relative to the rigid body representing the segment one wish to study. Thereafter, at every examination, the "fictive" points simply "follow" the segment, and the translational vector (MTPM) can be calculated.
To investigate instant load induced micromotion across the osteotomy, so called inducible displacement, one-leg standing RSA examinations were carried out immediately after the normal supine examination. The relative movement between these two examinations thus reflected the current stability of the osteotomy (26).
Rotation and translation is presented as right sided results, meaning that the results for the left sided osteotomies have been transformed to right sided. Rotation of the rigid body, in the proximal segment, around the 3 axes (X, Y, Z) is expressed with (+) and (-) for positive, respectively negative rotation. Positive rotation around the X-axis results if the rigid body tilts anteriorly, positive rotation around the Y-axis equals internal rotation, and rotation around the Z-axis results in valgus (+), and varus (-).
The translation values represent translation of the center of gravity of the rigid body along the 3 axis, X-axis being medial-lateral, Y-axis being proximal-distal and the Z-axis being anterior-posterior.
Rotation and translation results are all presented as right sided results, meaning that the results for left sided osteotomies has been transformed to right sided.
Precision of the method was found as the measuring error of scanned images from 9 double examinations on 9 randomly chosen patients. The patients stepped down from the examination table between examinations.

Roentgenographic examinations

Roentgenograms of the hip, knee and ankle, with the patient in standing position, were performed preoperatively for evaluation of HKA-angle and pre-operative planning, and after three months, one and two years postoperative (27).
Arthritis were graded after Ahlbäck preoperatively and after two years (28).

KOOS

Knee injury and outcome score (KOOS) is a clinical score intended for evaluation of follow-up of physically active patients after knee injury and the consequences of knee osteoarthritis (29-32), and has also been used in the follow-up after open wedge osteotomies with the hemicallotasis technique (33) . The questionnaire is self administered and comprises 5 subscales: Knee related symptoms (symptom), pain, sport & recreation (sport), activity of daily living (ADL), and quality of life (QOL). On each of the subscales 100 points equals zero problems whereas 0 points equals extreme problems (34).
An improvement of 10 points in a subscore was considered clinical significant.

Postoperative regimen and follow-up

Patients were allowed 6 weeks of limited weight bearing (20 kg) with the leg in a splint allowing free flexion in the knee joint. After 6 weeks, full weight bearing was commenced.
RSA examinations were obtained 1-3 days postoperatively and 3, 12 and 24 month postoperative. After the 12 month examination, the internal fixation was removed and both a normal and a stress RSA examination, with the patient standing on one leg, were performed. This was used to asses the displacement induced by one-leg standing.
KOOS scores were completed by the patients at inclusion, after 6 weeks, 3, 12 and 24 months.

Statistics

Our primary outcome was the average MTPM, after one year, of fictive points placed at the tip of the medial and lateral tibial eminence. The study was designed to find a difference in MTPM of 1mm with three groups and an expected standard deviation of 0.5mm and a risk of type 1 error of 5% and a power of 80%. To find such a difference, six patients were needed in each group. To accommodate for eventual dropouts we included 15 in each group (3 x 15).
MTPM was tested with non-parametric Kruskal-Wallis's test. Secondary outcomes: rotations and translations after one year, were tested with ANOVA with robust variance estimation. Differences in arthritis grading and KOOS subscores between groups were tested with Kruskal-Wallis's test. A p-value below 0.05 was considered significant.

RESULTS

One patient (Calcibon group) died before the one-year control of unrelated causes and one missed the one year control before hardware removal as the hardware was removed at another hospital, and one patient followed the study plan until the one year control after which he didn't want to complete the study because of other morbidities. Four set of images were excluded because of too high ME of rigid body fitting (loose markers and/or poor image quality). Furthermore another six set of images was excluded because of too high condition number.

After one year only minor non significant migrations were found in all groups. MTPM was highest for the local autograft bone group and lowest for the Calcibon group (table 3). Rotations and translations after one year were all below one degree for the rotations and one millimeter for the translations regardless of bone grafting material (table 4).

Looking at MTPM over time all three groups displayed most of their migration within the first three months (fig. 3). Thereafter slightly different, non significant, migration patterns are displayed: Calcibon is more stable in the first three months but demonstrates discrete migrations at the two year control. The local bone autograft group migrates the most during the first year after which it seems to stabilize. The iliac crest bone autograft group stabilized after the 3 month control.

Inducible displacement after hardware removal displayed average movement below our detectable limit for MTPM and maximum movement below 1mm, indicating that the osteotomies had stabilized (table 5). The one osteotomy with the highest inducible displacement moved 0.61mm (Id 608, Calcibon group). At time of hardware removal we suspected that a deep slow infection had evolved at the osteotomy. Therefore the osteotomy was evacuated. No infection was found. The following year further 0.5mm of migration was measured.

Over the course of the study the HKA angle remained stable in all three groups (table 6), however one patient in the ICPC group had a displaced lateral fracture and had lost correction already at the 3 months control and continued to loose correction after one and two years, explaining the wider range for the ICPC group. This patient was excluded from the RSA-analysis since the CN number was to high. But disregarding the high CN number, RSA revealed continuous migration for this patient with MTPM of 3.31, 4.79 and 5.14 after three months, one and two years respectively.

Clinically, improvements were seen in all subscores after one year, especially in the pain, ADL, and sport scores. The Calcibon group revealed the lowest scores in all subscores at all time points apart from ADL after 6 weeks where the iliac crest group had the lovest score. Only the QOL score at two years for the Calcibon group were significantly lower than the local graft group ($p = 0.047$) (Table 7).

Overall the radiographic assessment of arthritis (Ahlbäck) had improved significantly after two years (table 8). The improvements in the local bone autograft group were however not significant – in spite of the better clinical scores at two years.

DISCUSSION:

The main purpose of this study was to evaluate the stability of the open-wedge osteotomy construct, as measured with RSA, with three different bone graft materials: Local bone autograft, iliac crest bone autograft and injectable calcium phosphate cement (Calcibon®). The study was designed to reveal a difference of 1 mm in MTPM after one year which we considered to be a clinically significant change in osteotomy movement. We did not find such clinically relevant difference as the biggest difference was 0.8 mm. We found only minor migrations regardless of bone grafting material. All three groups migrated the largest part during the first three months where Calcibon stabilized the osteotomy the most, but not statistically significant.

After one year the hardware was removed and loaded RSA was performed to assess inducible displacement. This revealed that the osteotomies generally were stable without supporting osteosynthesis, apart from one that had been evacuated due to suspected deep infection.

In a previous biomechanical study we found that ICPC stabilized an OW-HTO under loading mimicking normal walking. But we did also find that the implant itself seemed to be stable enough to withstand the loadings found during walking (own submitted results). This might be the reason why the migration in the two bone groups also was small in the present study. Another explanation could be the biological reaction to Calcibon: In biopsies retrieved at time of hardware removal we found that Calcibon induced a mixed soft tissue response with fibrous covering of the Calcibon surface (own unpublished results). This might influence the stability of the osteotomy. Ideally, early weightbearing would induce the optimal amount of micro movement securing healing as investigated by several groups (35-37).

The patients were aligned to satisfying 4° of valgus and kept the alignment throughout the study period.

Clinically outcome scores revealed improvements in all KOOS subscores at the two year control. Surprisingly, the Calcibon group displayed the lowest scores at almost all timepoints in all subscores, especially knee related symptoms and quality of life, in spite of the lower osteotomy migration and improvements in the arthritis score. This could also be explained by the mixed soft tissue response of ICPC.

Generally, when discussing bone grafts for OW-HTO, the options are autograft, allograft or synthetic bone substitutes. Autograft, mainly from the iliac crest, is considered gold standard (1;3-5) but shortcomings include limited availability and harvest of autograft induces donorsite-morbidity, as 30-40 % of patients report complaints of pain at the donorsite, 6 month after operation (7). Allograft does not induce donor-site morbidity but carries a minor risk of transfer of infectious agents. Therefore synthetic bone substitutes have been introduced. Synthetic bone substitutes should ideally be biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective (8). Several authors have investigated the healing response of different graft materials in open-wedge osteotomies. Hernigou used a full bony wedge from the iliaca crest in the osteotomy gap without internal fixation. He observed 11/93 with loss of correction due to fracture of the lateral cortex. With the introduction of internal fixation no collapses was observed (3).

In 50 operations, with full thickness iliac crest grafts, Devgan reported no non-unions but one case of collapse of the bony graft, resulting in loss of correction (4)., Lobenhoffer introduced the use of “local cancellous bonegraft” in minor corrections (<10°) and wedges from either iliac crest or hydroxyappatite/tricalciumphospate in larger corrections. In 101 operations with the Arthrex® osteosynthesis plate stabilization there were six cases of non-union and associated implant-failure. After surgical modifications, including exchange of osteosynthesis to a plate fixator with locked bolts (TomoFix™), no further cases of non-union were noted (1). Koshino found no cases of

collapse after ten years, in 21 cases treated with open-wedge HTO with a combination of hydroxyappatite-wedges and autologous fibular bonegraft (6). Staubli et al (11) did not use bonesubstitutes and argued that the osteosynthesis fixation devices yields sufficient stability. In 92 operations they reported 2 cases of delayed union and loss of correction after removal of osteosynthesis material before 12 month. Hernigou filled the osteotomy gap with acrylic cement and reported two delayed healing, one non-union out of 245, and no problems with succeeding TKR (9).

Some limitations to the current study should be noted. In theory, the influence of eventual confounders is minimized in a randomized study as the current. Eventual confounders as smoking and weight were evenly distributed between groups. But a large patient material would have improved the power of the study. The size of the study population was unfortunately slightly diminished, and dropouts were unevenly distributed as more patients dropped out in the iliac crest bone autograft group. Still, with more patients in the study, we would probably still find differences in migration below clinical relevant migration. Osteotomy stability is only a surrogate parameter to evaluate the healing. But it is well known that stability is of major importance for the bony healing and that delayed healing can lead to loss of correction, i.e. recurrence of varus malalingment. RSA is generally accepted as the method to determine eventual migration and our results are in concordance with the findings by Magyar et al. (23). All patients in the present study were operated and rehabilitated according to same protocol which should optimize group comparability. Differences in migration and clinically outcome therefore can be attributed to the choice of grafttype.

One of the major goals of improved methods for OW-HTO is to achieve full weight bearing immediate postoperatively: With the hemicallotasis technique where immediate weight bearing is allowed, W-Dahl et al. found that large improvements in clinical outcome (KOOS) occurred already during the immediate postoperative period following osteotomy (33). From the present study we can not conclude if immediate weight bearing can be tolerated, but the findings suggest that, regardless of bone graft materials, stable healing of the osteotomy is achieved.

CONCLUSION:

In this randomized study, including 45 patients followed for two years, only minor migration, translations and rotations of the osteotomy were revealed, regardless of bone grafting material. With a stable implant and six weeks of partial weight bearing, it seems that no further grafting materials, besides local autografting, is needed to achieve solid bone consolidation following open-wedge HTO.

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Figure legends

Fig. 1
Osteotomy before (a), and after grafting with local bone autograft (b), iliac crest bone autograft (d), and ICPC (e)

Fig. 2
Osteotomy after RSA-preparation, and the 3D-coordinate system with arrows showing the direction of positive rotation around the axis. The tantalum markers connected with yellow lines, defines the rigid body representing the proximal segment above the osteotomy. The red markers represent the segment distal to the osteotomy.

Fig. 3
Boxplot illustrating maximal total point motion (MTPM), meaning the length of the translational vector, in mm, of the tibial eminence. The box represents the interquartile range with median line in the box. Whiskers represent non-outliers min-max. Dot represents outliers (<3 inter quartile range)

Tables

Table 1
In- and exclusion criterias

Inclusion criterias

- Medial arthritis, Ahlbäck gr. 1-2
- Signed informed content

Exclusion criterias

- Age > 18 years or < 65 years
- Medication with corticosteroids or NSAID
- BMI > 35
- Previous surgery in lateral knee compartment
- Arthritis secondary to fracture
- Lack of informed content

Table 2
Patient characteristics

	All n = 45	Local bone autograft n = 15	Iliac crest autograft n = 15	Calcibon n = 15
Sex (Women/men)	11 / 34	4 / 11	4 / 11	3 / 12
Age mean (years)	48.0	50.5	47.8	45.6
SD	8.1	7.8	9.6	6.1
Weight mean	86.6	83.6	86.0	90.0
SD	12.7	13.2	14.6	9.8
BMI mean	27.7	27.3	27.4	28.3
SD	3.5	3.3	4.0	3.2
Smokers	16/45	7/15	4/15	5/15
Ahlbäck gr.	1.3	1.1	1.4	1.3
Range	1- 3	1 - 2	1 - 3	1 - 3
HKA mean (°)	175	174	177	175
Range	168 - 182	168 - 179	171 - 182	168 - 182
Peroperative Fracture None/undisplaced/displaced	32/10/3	9/5/1	13/1/1	10/4/1
Gap size (mm)	10.1	10.8	8.8	10.7
Range	5 – 17.5	6.25 – 17.5	5 - 15	6.25 - 15

Table 3
Precision of measurements, presented as measuring error and 95% confidence interval, of double examinations on 9 randomly chosen patients operated with open-wedge osteotomy

Migration	Mean error, 95 % confidence limits
X-rotation, dgr	0.06° +/- 0.14
Y-rotation, dgr	0.03° +/- 0.09
Z-rotation, dgr	0.03° +/- 0.11
X-translation, mm	0.03 +/- 0.07
Y-translation, mm	0.07 +/- 0.06
Z-translation, mm	0.01 +/- 0.06
MTPM, mm	0.19 +/- 0.07

Table 4
Maximal total point motion (MTPM) of the tibial eminence in mm, after one year

MTPM (mm) after one year	N	Mean	SD	P-value
Local bone autograft	12	1.90	1.37	
Iliac Crest bone autograft	9	1.35	1.20	0.121
Calcibon	12	1.11	1.11	

Table 5
Rotations (dgr.), and translations (mm) after one year.

	Local bone autograft		Iliac crest autograft		Calcibon		P-value
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
X-rotation	-0.87	-1.66 - -0.08	-0.76	-1.82 - 0.29	-0.65	-1.16 - -0.15	0.87
Y-rotation	0.27	-0.51 - 1.06	0.34	-0.11 - 0.79	0.05	-0.28 - 0.38	0.49
Z-rotation	-0.01	-0.98 - 0.96	0.04	-0.60 - 0.67	-0.67	-1.44 - 0.11	0.28
X-translation	-0.13	-0.90 - 0.64	-0.17	-0.73 - 0.40	0.35	-0.03 - 0.74	0.19
Y-translation	-0.77	-1.40 - -0.14	-0.64	-1.15 - 0.14	-0.54	-0.98 - -0.09	0.80
Z-translation	-0.59	-0.97 - -0.21	-0.46	-0.98 - 0.07	-0.37	-0.64 - -0.10	0.58

Table 6
Inducible displacement after hardware removal, MTPM (mm)

Group	N	Mean	95% CI	Min	Max	P-value
Local bone	12	0.13	0.08 -0.18	0.05	0.28	
Iliac crest	11	0.10	0.06 -0.14	0.03	0.21	0.64
Calcibon	13	0.14	0.06 -0.23	.003	0.61	

Table 7
Axial alignment before and after osteotomy

	All **n = 45**	**Local bone autograft** **n = 15**	**Iliac crest autograft** **n = 15**	**Calcibon** **n = 15**
Preoperative HKA **Mean (range)**	175 168 - 182	174 168 - 179	177 171 - 182	175 168 - 182
3 months HKA **Mean (range)**	184 177 - 192	184 180 - 187	185 180 - 190	184 177 - 192
1 year HKA **Mean (range)**	184 174 - 190	183 178 - 186	184 180 - 187	183 174 - 190
2 years HKA **Mean (range)**	184 172 - 190	184 180 - 187	185 182 - 190	182 172 - 190

Table 8
Knee injury and osteoarthrtitis outcome score (KOOS).

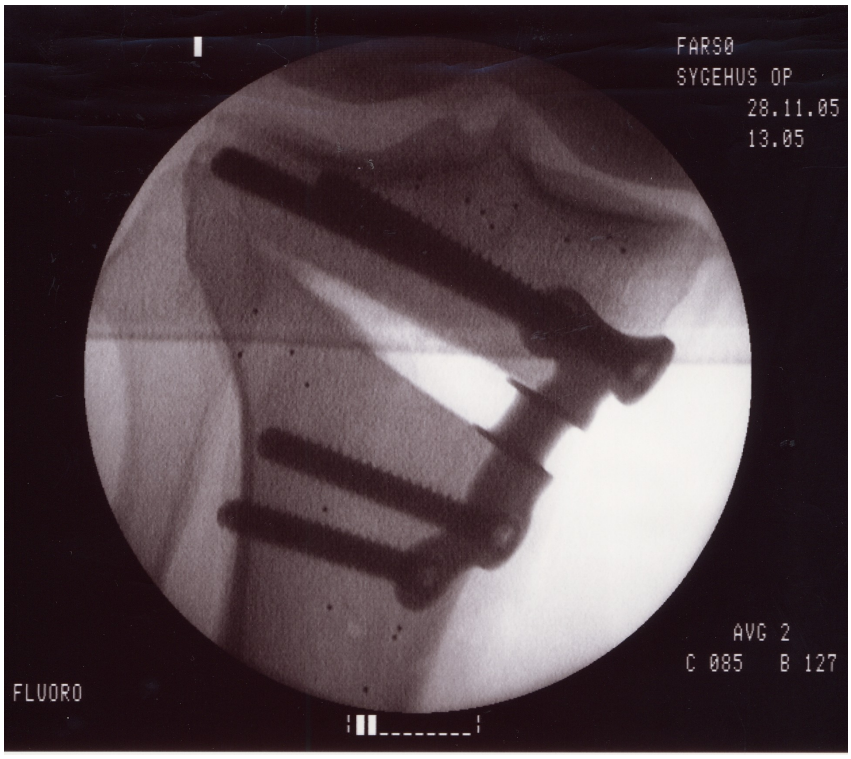
		Visit									
		Inclusion		6 weeks		3 months		12 months		24 months	
Subscale	Group	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean SD	N	Mean (SD)
Symptom	Local	15	61 (16)	15	70 (17)	14	68 (19)	15	78 (19)	14	74 (25)
	Iliac crest	15	66 (17)	14	72 (16)	15	67 (14)	15	75 (18)	14	73 (22)
	Calcibon	15	61 (17)	15	61 (23)	15	60 (21)	14	69 (20)	14	67 (17)
Pain	Local	15	52 (15)	15	70 (18)	14	66 (16)	15	79 (20)	14	78 (23)
	Iliac crest	15	53 (14)	12	68 (19)	15	56 (16)	15	70 (21)	14	67 (24)
	Calcibon	15	49 (15)	14	64 (21)	15	56 (24)	14	66 (27)	14	63 (27)
ADL	Local	14	58 (16)	14	65 (15)	14	68 (16)	15	83 (18)	14	80 (23)
	Iliac crest	15	58 (15)	9	57 (17)	15	63 (17)	15	74 (18)	14	70 (24)
	Calcibon	14	58 (20)	14	60 (21)	15	62 (22)	14	69 (27)	14	67 (26)
Sport	Local	15	26 (16)	9	9 (11)	14	29 (19)	15	52 (26)	14	53 (25)
	Iliac crest	13	20 (16)	10	15 (24)	15	25 (18)	14	42 (28)	14	42 (28)
	Calcibon	14	22 (13)	14	11 (16)	14	21 (21)	13	35 (31)	14	38 (32)
QOL	Local	15	34 (18)	14	35 (13)	14	38 (15)	15	62 (23)	14	66 (26) *
	Iliac crest	15	32 (14)	11	32 (16)	15	42 (18)	15	55 (29)	14	50 (27)
	Calcibon	15	30 (14)	15	30 (20)	15	35 (20)	14	39 (22)	14	40 (25) *

* QOL after 2 years with statistically significant difference (*) between Calcibon and Local bone autograft.

Table 9
Grade of arthritis before and 2 years after operation

	All **n = 45**	**Local bone autograft** **n = 15**	**Iliac crest autograft** **n = 15**	**Calcibon** **n = 15**
Preoperative Ahlbäck gr.	1.3	1.1	1.4	1.3
Range	1- 3	1 - 2	1 - 3	1 - 3
2 years Ahlbäck gr.	1	1.1	0.9	1.0
Range	0 - 3	0 - 3	0 - 3	0 - 3
P-value	0.001	0.582	0.006	0.039

Figures



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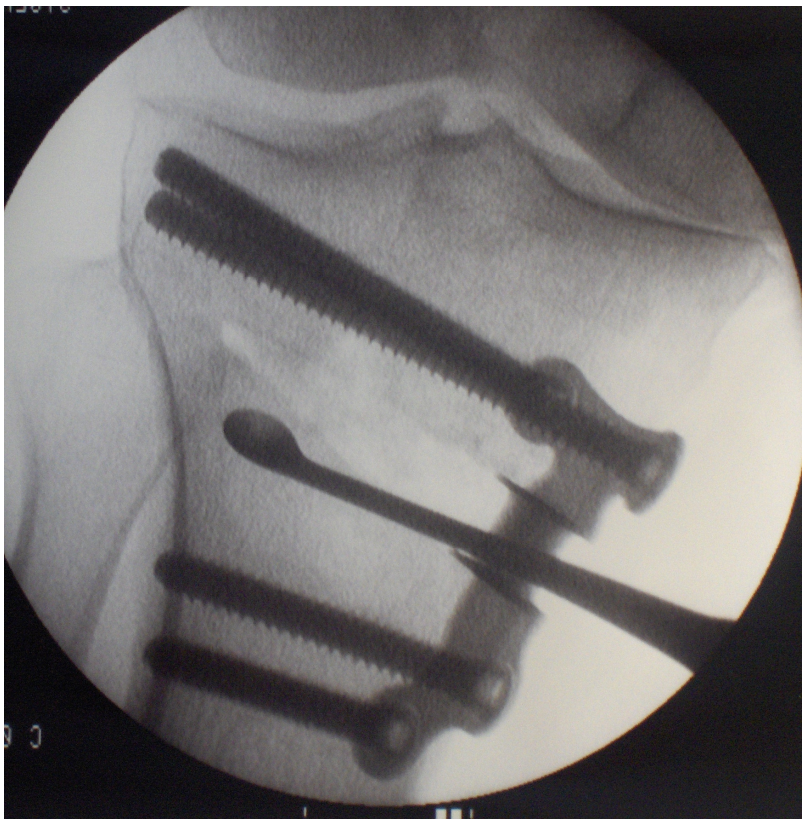

Fig 1b

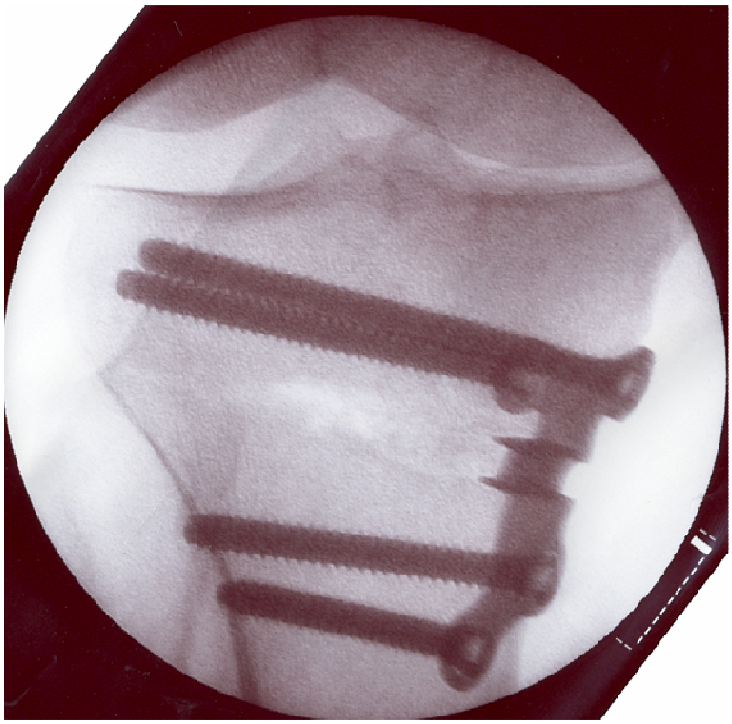

fig 1c

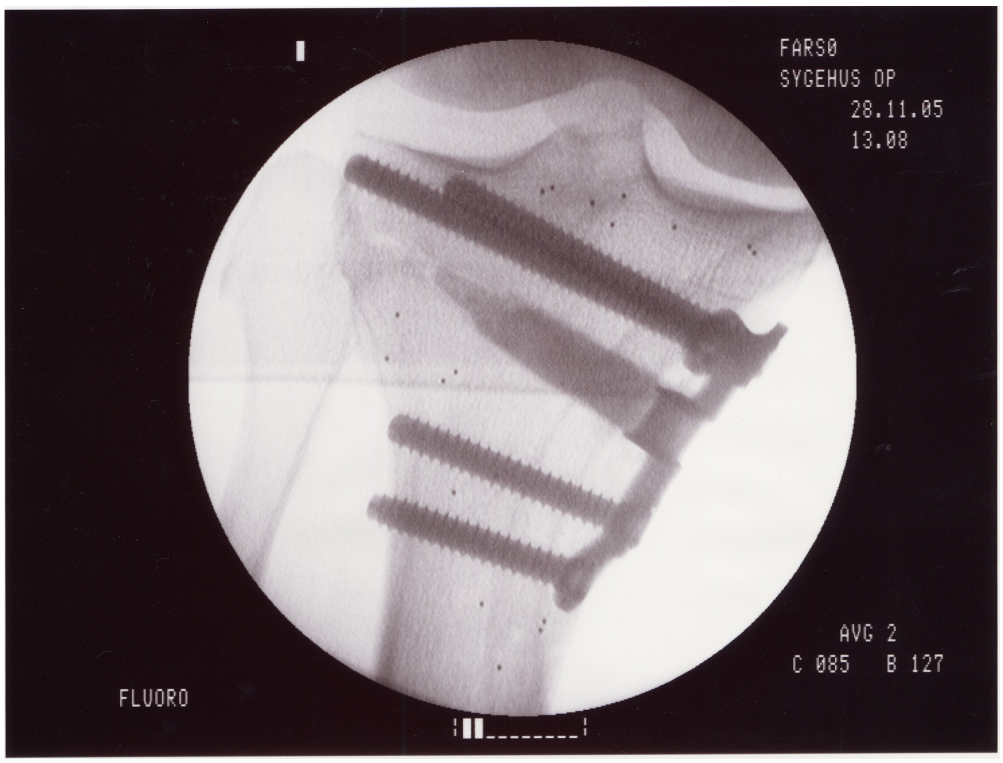
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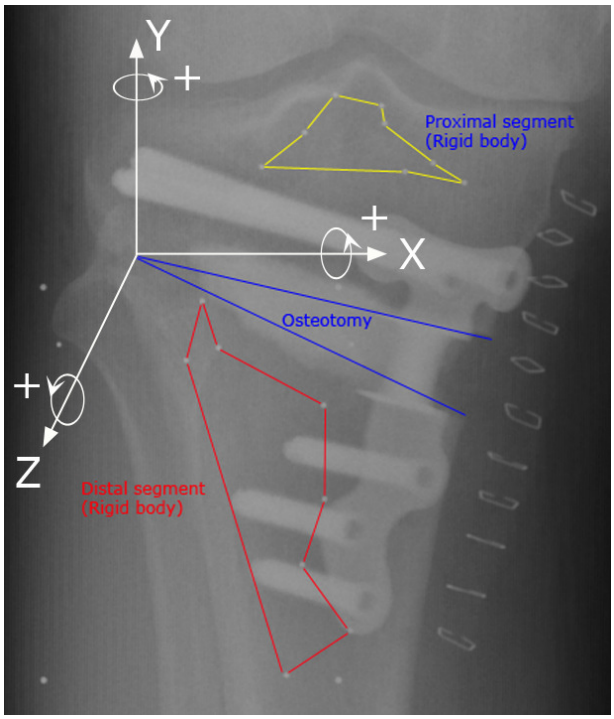
Fig. 1d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+
Proximal segment
(Rigid body)
+
X
Osteotomy
+
Z
Distal segment
(Rigid body)

Fig. 2

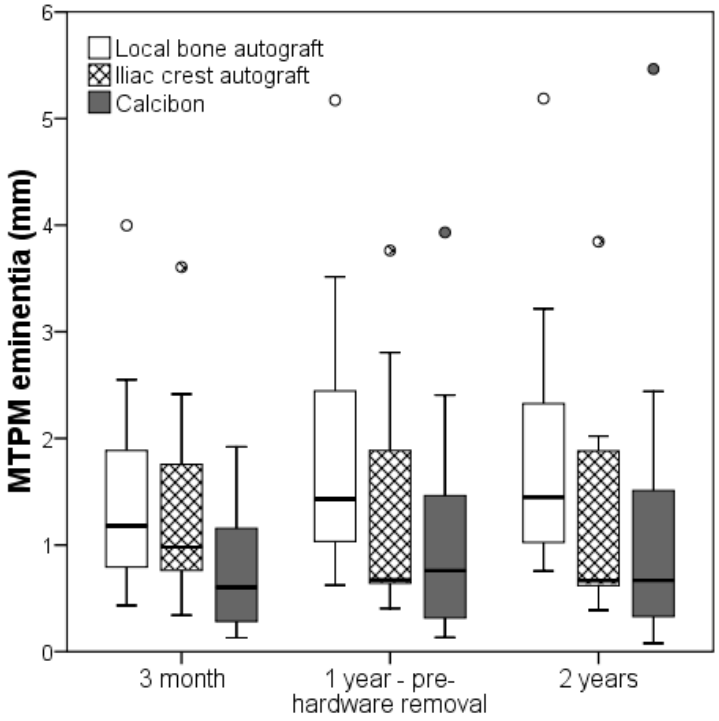
Local bone autograft
Iliac crest autograft
Calcibon
MTPM eminentia (mm)
0
1
2
3
4
5
6
3 month
1 year - pre-hardware removal
2 years

Fig. 3

Paper III

Open-wedge osteotomy - Histomorphometric evaluation of three bone graft materials
A randomized controlled study

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Abstract

INTRODUCTION

Open-wedge high tibia osteotomy is an established joint preserving treatment of medial knee osteoarthrosis. The procedure does, however, leave a bone-gap which must heal properly. In a randomized controlled study, we investigated histological bone healing of tree different bone graft materials: Local bone autograft (trabecular bone chips released within the osteotomy gap), iliac crest autograft and the injectable calciumphosphate cement (ICPC) Calcibon®.

MATERIALS AND METHODS

One year postoperatively, during plate removal, cylindrical core biopses were retrieved for histology. Quantitave histomorphometry was performed using stereological software in three regions of interest: Trabecular bone adjacent to defect, osteotomy gap, and cement-bone interface at the osteotomy gap for the Calcibon group. Bonevolume fractions and trabecular thickness was estimated. In the Calcibon group, bone and fibrous tissue covered surface fractions of the cement-bone interface was estimated.

RESULTS

No statistically significant differences were found between the two bone graft groups regarding bone volume fraction (BV/TV) and trabecular thickness. BV/TV of the defect was 24 % in the local bone autograft group and 27 % in the iliac crest autograft ($p = 0.44$). Trabecular thickness was 114µm mm and 97µm ($p= 0.40$) in the local and iliac crest autograft groups respectively. ICPC induced a mixed bone and soft tissue healing response with bone ingrowth to 45 % of the cement surface and fibrous covering of 55 %.

CONCLUSION

Local bone autograft healed to the same quality of bone as iliac crest bone autograft. Calcibon was largely unresorbed after one year in the tibial osteotomy gap, and exhibited both bone and soft tissue ongrowth.

KEY WORDS

Tibial Osteotomy, Osteoarthrosis, Bone graft materials, Bone healing, Histomorphometry

Background

In the recent years medial open-wedge HTO has become popular in the treatment of young active patients with medial knee osteoarthritis with varus malalignment. The methods used are, either distraction by hemicallostasis with external fixation, or immediate opening supported by internal fixation (1-4). The latter, however, leaves a bone defect, with a medial opening. To secure healing of the osteotomy, different bone graft materials are suggested by various authors. Autograft is considered the gold standard since it secures healing (1;3;5-7) but also includes disadvantages, i.e. limited availability and donor-site morbidity (8). Another alternative is allograft which entails a minor risk of virus transfer (9).

Several bone substitutes have been introduced for open-wedge HTO, either alone or in combination with auto- or allograft: Hydroxyappatite (HA), Beta Tricalcium Phosphate and acrylic cement (1;6;7;10-13).

In a randomized clinical trial, Dallari et al.found that platelet gel and bone marrow stromal cells improved the osteogenic potential of lyophilized bone chips when investigated after 6 weeks. Complete clinical function were found regardless of method after 12 month (14).

Delayed healing is reported in up to10 % of operations performed, with or without grafting (1-3;5-7;10-13). Delayed healing and non-union is associated with implant failure and loss of correction. With improved bone grafting materials and safe postoperative rehabilitation regimens these problems could be solved. Injectable calcium phosphate cement (ICPC) might be a beneficial bone substitute for HTO bone gaps. The material offers osteoconduction and initial high compressive strength (15-18) and thereby, enhances primary stability (Own submitted data).

The aim of the present histomorphometric study was to investigate the biological healing response, of three different bone grafting materials, i.e. local bone autograft (trabecular bone chips released within the osteotomy gap), iliac crest bone autograft and the injectable calciumphosphate cement Calcibon®. We hypothesized that iliac crest autograft, when compared to local autograft, would result in improved healing with bone volume fractions and trabecular thickness comparable to normal bone. We also hypothesized ICPC to be incorporated in bone tissue and gradually resorbed without any soft tissue reaction.

MATERIAL AND METHODS

Study design

A randomized controlled trial was carried out on patients who had an open-wedge osteotomy performed. The patients were randomized to the following intervention groups:

7. Local bone autograft.
8. Iliac crest bone autograft.
9. Calcibon®

After ostetosynthesis of the osteotomy, sealed envelopes was opened in the operating theater, revealing the random assignment to either of the intervention groups.
The study was conducted at Farsø Hospital, Orthopaedic Division, North Denmark Region. The study was approved by the Ethics committee for the Viborg and Northern Jutland counties, Denmark, Study no.VN 2004/53, and registered at Clinical Trials Gov.

Patients

In the period 10th December 2004 to 12th June 2006 71 patients had a corrective open-wedge osteotomy performed at our clinic. Of these, 61 were unilateral medial open-wedge osteotomies and met the inclusion criteria's (Table 1). 49 patients accepted to be included in the project and signed informed consent. Four were excluded after inclusion and signed informed consent but before operation: one had rapid progression of arthritis necessitating total knee replacement, one was operated at another clinic, one was excluded because of interim competing disease and one withdrew consent to participation.
Thus 45 patients were randomized.

Osteotomy

Patients were operated in supine position using a tourniquet. The osteotomy was initiated with saw and completed with osteotome. Opening of the osteotomy was performed with the bone spreader and osteosynthesis was performed with a titanium spacer plate and 6mm non-locking titanium screws (Dynafix® VS™ Osteotomy System, Biomet). (Fig.1a – tom osteotomi).

Grafting procedures of bone graft materials

4. Local bone autograft: Using a curette, the cancellous bone from the two adjacent cut surfaces was scooped out in the osteotomy defect creating a loosely woven bone network.
5. Iliac crest bone autograft: With minimally invasive technique, milled, cancellous bone, corresponding to the volume of the osteotomy, was harvested from the iliac crest using the Accumed® Bone Graft Harvesting System (Acumed®, Oregon, USA). The height (h) and depth (2*r) of the osteotomy, considering the gap a wedge, was used to estimate the gap volume ($V \sim \pi * r^2 * h/2$).
6. ICPC: The cement was mixed and injected into the osteotomy defect with a syringe. Care was taken to secure macroscopic filling of the osteotomy.

Injectable calcium phosphate cement

We used Calcibon® (Biomet Merck GmbH) which is a synthetic, biodegradable, calcium phosphate based bone substitute, that can be applied directly and hardens at body temperature. After six hours

the compressive strength is comparaple to cancellous bone, and after three days the final compressive strength of up to up to 60 MPa is reached. It is intended for filling of metaphyseal, cancellous bone defects. The material is mixed during the operation from a liquid and a powder part. The powder part consist of 58 % α-TCP (Tri Calcium Phosphate), 8.5 % PHA (Precipitated Hydroxyappatite), 25 % CaHPO4 (Calcium Phosphate) and 8.5 % CaCO3 (Calcium Carbonate). The chemical composition and crystalline structure of the cured material mimic the mineral part of natural bone (16;17;19).

Postoperative regimen

The first six weeks, the leg was in a hinged brace allowing free flexion in the knee joint, and limited weight bearing (20 kg) were prescribed. Hereafter full weight bearing was commenced.
Bony healing was evaluated with x-ray after three and twelve month.

Biopsies

Sampling of biopsies

Biopsies were taken at time of hardware removal immediately after the 12 month control.
Plate and screws were removed through incision of the old cicatrice. With a 6 mm trephine, using fluoroscopy, a core biopsy crossing the osteotomy were acquired through the proximal of the distal screw holes, at an angle of approximately 45 ° on the longitudinal axis in the A-P plane, and central and parallel to the longitudinal axis in the side plane. (Fig. 1b and c)
The biopsies were gently pushed out of the trephine with the stiletto, and, to avoid longitudinal rotation, placed in a plastic straw. Until preparation the biopsies were kept at -20 °.

Specimen preparation

Thawed biopsies (Fig. 2a and b) were dehydrated in graded ethanol (70-100%) containing basic fuchsin. After dehydration each biopsy was embedded in methyl methacrylate. Using vertical sectioning technique (20;21) four 60-100 µm histological sections were cut from each biopsy with a microtome. The sections were surface counterstained with 2 % light green for 2 min, rinsed and mounted on glass (22). This preparation provided red staining for non-calcified tissue and green staining for calcified tissue. Different bone types (woven and lamellar bone) were discriminated by their morphological characteristics: Lamellar bone was defined by a highly organized lamellar and linear structure with flattened lamellar-oriented oval cells. Woven bone was characterized by a less organized structure with rounded cells and without any lamellar structure.

Histomorphometric analysis

Quantitative histomorphometry was performed using the stereological software newCAST (Visiopharm A/S, Hørsholm, Denmark). Regions of interest (ROI) were defined by an independent observer (Fig. 3a and 4a). Delineation of the regions was done with the aid of the software (4b).
Basically, a counting grid is placed with random orientation on the histological slices in the microscope. The grid can consist of points, and/or lines. Each point represents an area; thereby the number of points counted at each kind of tissue gives the total area of that tissue in the sample, from which the volume and volume fractions can be calculated. Each line has a given length, and from this tissue thickness and surface fractions can be approximated when line intercepts of the specific tissue is counted.

Autgraft bone groups (Fig. 3a-b)

ROI 1: Trabecular bone just adjacent to medial, metaphyseal, cortical bone.
ROI 2A: Osteotomy gap.
In the regions defined, initially, volume fractions of woven bone and lamellar bone, fibrous tissue and marrow space were quantified by point-counting technique.

$$\text{Tissue volume fractions} = \Sigma\text{Points tissue}/\Sigma\text{Total points}$$

With line-interception and point counting of the trabeculae, the mean trabecular thickness was estimated as the reciprocal value of BS/BV (Fig. 3b).

$$\text{Trabecular thickness} = 2/2*(p/l)*(\Sigma\text{Bone-intercepts}/\Sigma\text{bone-points})$$

p/l = number of test points divided by total length of test line.

Calcibon group (Fig. 4a-c)

ROI 1: Trabecular bone just adjacent to medial, metaphyseal, cortical bone.
ROI 2B: Bone-cement interface.
In ROI 1 the same parameters were used as in the bone specimens.
The surface area fractions of bone-covered cement, and non bone-covered cement, (primarily fibrous tissue), were quantified with line-interception technique (Fig. 4c) (21).

$$\text{Surface fraction} = \Sigma\text{Tissue intercepts}/\Sigma\text{Total intercepts}$$

Roentgen

Bone filling of the osteotomy was estimated by judging whether or not the osteotomy was filled in each one third from lateral to medial.
In the ICPC group it was noted whether or not cement was present and whether demarcation was present around the cement, or if the cement seemed to integrate with the bone.

STATISTICS

Means and standard deviations were calculated. Differences between groups were tested with one-way ANOVA in ROI 1. In ROI 2 only the two bone groups (local graft and iliac crest graft) were compared with t-test, since the majority of ICPC was still present and therefore defined the ROI. Fibrous tissue covering in demarcation or no demarcation groups were compared with t-test.
A p-value below 0.05 was considered significant.

RESULTS

Forty two biopsies were obtained (one had the plate removed at another hospital, one rejected plate removal and one had died of unrelated causes), six biopsies were of inferior quality, i.e. fragmented, broken or with unidentifiable ROI's, which left thirtysix well preserved biopsies suitable for histomorphometric evaluation. Patient characteristics are shown in table 2.

In all of the ICPC samples large amounts of ICPC was still present. The ICPC-bone interface was inhomogeneous and he ICPC was fragmented with a lot of inactive surfaces which by definition was not counted. The biologic active surfaces were either covered with bone or fibrous tissue, varying from 100 % bone cover to 95 % fibrous covering. More than half of the specimens had a fibrous tissue covering of 55 % or more (Table 3 and Fig. 5a-b).

Generally only sparse amounts of woven bone were found. The vast majority of bone tissue in the two ROI's was lamellar trabecular bone. In the bone autograft groups sparse amounts of fibrous tissue was present. No statistically significant differences were found in BV/TV and trabecular thickness between the two bone autograft groups in either ROI. BV/TV of the defect was 24 % in the local bone autograft group and 27 % in the iliac crest autograft group ($p = 0.44$). Mean trabecular thickness in the defect was 114µm and 97µm ($p= 0.40$) in the local, and iliac crest bone autograft groups respectively (Table 4).

The total mean trabecular thickness in the defect (106µm (SD 50), $n = 24$) was significantly lower ($p = 0.021$) than the total mean trabecular thickness of the superficial trabecular region (139µm (SD 57), $n = 36$). However at group level no statistical significant differences were found between trabecular thicknesses of the defect and superficial trabecular region.

When comparing the superficial trabecular region (ROI 1) below the osteotomy gap, no significant differences was found in BV/TV and trabecular thickness between the three groups (table 5).

A prominent feature on roentgen was demarcation of the ICPC. After one year four patients had demarcation around the ICPC. All of these had high levels of fibrous tissue covering, and none of the completely bone covered cement interfaces (n=3) displayed demarcation on roentgen (table 3). Mean fibrous tissue covered fraction of the patients displaying demarcation were 66% (SD = 28) as opposed to 26%, (SD = 32) in patients with well integrated ICPC ($p = 0.072$, t-test).

In both the autograft bone groups, 10/12 had complete filling of the osteotomy gap after 12 month. No correlation could be found between the degree of osteotomy filling, and BV/TV or trabecular thickness.

DISCUSSION

In this randomized controlled study we investigated three different grafting materials in high tibial open-wedge osteotomies. Graft healing was evaluated, in core biopsies from the central part of the osteotomy, at one year postoperatively by quantitative histomorphometric analysis. In the two bone autograft groups no statistically significant differences was found, when comparing bone volume fraction and trabecular thickness. This was the case both in the adjacent bone and in the defect. The adjacent bone was found to be similar in all three groups, and comparable with the bone structure in the defects at group level, but if data were pooled from all three groups the trabecular thickness in the defect was lower than in the adjacent region. Unfortunately we do not know the preoperative histomorphometric data for bone quality, which would have been interesting. Comparing our trabecular thickness data with other studies, our findings are lower, but in acceptable concordance with the findings of other studies (23;24).

In the ICPS group most of the ICPC was still present in the osteotomy gap, and more than half the ICPC specimens had more than 50 % covering of the cement surface with fibrous tissue.

In a previous biomechanical study we found amplitudes of approximately 0.7 mm when ICPC was used as void filler (Submitted data). According to Claes et al. this is probably approaching the limit for a healthy bone healing environment (25). Davies (26) points out that stable bone bonding occurs on sufficiently stable porous surfaces with undercuts and a complex three dimensional structure, like that provided by the demineralized collagen network during bone resorbtion, which lack after resorbtion of ICPC. So, one might speculate that the filling of the gap with ICPC, results in small but mechanically fragile interfaces, with relative pronounced strain, inhibiting cement resorption and bone apposition. We did observe fibrous tissue reaction, at the bone-ICPC interface, which might be the result of harmful amplitudes resulting from weight bearing during the preceding period of time. But in the bone autograft groups only minimal fibrous tissue was present, and they have been exposed to approximately the same loading pattern.

Some relationship was found between the presence of radiographic demarcation around the ICPC and the presence of fibrous covering on the ICPC surface. Demarcation is easily noted on roentgen and to some extent gives information if remodeling is occuring.

In previous experimental studies ICPC was remodeled, although slowly to bone tissue without soft tissue reaction i.e. there was no fibrous tissue as opposed to our findings (15-17). In experimental and clinical studies of fractures of the lateral tibial condyle, augmentation with injectable calcium phosphate cement gave comparable or better initial stability securing better final reduction, when compared to bone auto- or allograft. Histological, slow remodeling to bone was found (18;27-29).

When discussing bone grafts for open-wedge HTO, the several options have been reported including autograft, allograft, acrylic cement and synthetic bone substitutes, which have been used either alone or in combination to fill the osteotomy-gap (1;6;7;10-13). Autograft, mainly from the iliac crest, has previously been considered as gold standard (1;3;5;6), however, shortcomings include limited availability and donorsite-morbidity, with as much as 30-40 % of patients reporting complaints of pain at the donorsite, 6 month after operation (8). Allograft does not induce donor-site morbidity but carries a minor risk disease transfer. To accommodate for the needs synthetic bone substitutes have been introduced, the perfect bone substitute being biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective (9).

Clinically Koshino et. al. studied porous hydroxyapatite wedges as bone grafting material in open-wedge HTO. They found no resorption as judged by densitomtry but bone ingrowth progressed slowly; 70 % of the pores were filled with bone in a in a distance of 300 µm from the HA-bone interface.

Van Hemert et al. evaluated a β-tricalcium phosphate ceramic (ChronOS™ - Synthes) as either granules or wedge and found that it completely was completely resorbed and was no longer visible on X-ray in 85 % after one year (13). ChronOS™ was also studied by Gaasbeek et al. who found a good correlation between the x-ray findings and histological findings. They found that in 13/17 biopsies the original β-TCP was still present, 6 of these 13 with relative large areas of β-TCP. No infections or non-unions were encountered and all osteotomies were completely consolidated at 12 months (11).
Different biological bone healing stimulators have been investigated in HTO gaps. Dallari et al. found that platelet gel and the combination of platelet gel and bone marrow stromal cells increased the osteogenic potential of lyophilized bone chips after six weeks. However after 12 month all patients had complete clinical and functional evidence of healing (14).
Aryee et al. reported varying stages of bony consolidation in a study with 3 groups: no augmentation, HA/TCP, and HA/TCP+Platelet Rich Plasma (PRP). In open-wedge HTO augmented with HA/TCP wedges the HA/TCP wedge remained undissolved with partial bony ingrowth Full depth samples from unaugmented osteotomies showed mature lamelliform bone. No clinical differences were found between the groups. They conclude that augmentation with HA/TCP with or without PRP is not recommended (30).
Previously we have demonstrated that the injectable calcium phosphate cement Calcibon®, as a supplement to internal fixation, stabilized the HTO construct in cyclic axial loading and axial load-to-failure in cadaver- and composite tibia-models (Submitted data). It therefore seemed potentially beneficial to use ICPC as a graft material with the benefit of allowing earlier weight bearing due to a more stable osteotomy construct. The present study on the other hand suggest limited benefits since the protracted remodeling seems to induce a soft tissue response with could be delaying the bone remodeling process.
In the present clinical study all of the biopsies were acquired at the same time point of one year postoperatively, when the osteotomy was radiologically healed and the plate could be removed. To investigate the degree of new bone formation during the healing process at defined time intervals we could have used fluorochrome labeling with tetracycline and/or acquired serial biopsies. Due to ethical considerations this approach was not included in the study. To minimize trauma and risk of weakening the healed osteotomy, the biopsies were obtained from the central part of the osteotomy where both the bone density, and probably also the loading, is lower than in the periphery. Bone remodeling might progress more slowly in the central part of the osteotomy, and it is possible that we would have found a more active and “healthy” bone-cement interface in the periphery due to beneficial mechanical stimulation. But also the opposite could be the result since to much mechanical stimulation induces a soft tissue reaction and impaired healing.

CONCLUSION

Both local bone autograft and iliac crest bone autograft appear to heal and remodel uniformly based on bone volume fraction and trabecular thickness measurements. The injectable calcium phosphate cement Calcibon® on the other hand only remodels slowly and induces a varying soft tissue response which could be impair the remodeling process. These findings warn on the use of ICPC in open-wedge HTO.

Acknowledgements – Disclosures

The authors wish to thank: The study was financially supported by the following non-commercial institutions: WSF – Western Denmark Health Research grant of Aarhus University, Danish Rheumatism Association, The Spar Nord Foundation, Aarhus University Research Foundation, and North Jutland Medical Association Research Foundation. The study have benefited from institutional research support from the following company with commercial interests in this research area: Biomet Denmark

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Figure captions

Fig. 1a
Open-wedge osteomy stabilized with titanium plate and screws

Fig. 1b
Core biopsies were acquired with a 6 mm trephine under fluoroscopic guiding securing that the biopsy was crossing the osteotomy and placed centrally and aligned with the longitudinal axis of tibia. AP (top) and lateral view (bottom)

Fig. 2a and b
Thawed biopsies before preparation and sectioning - a) bone autograft b) Calcibon

Fig. 3a
Section of bone autograft specimen with ROI marked

Fig. 3b
Bone specimen with point counting technique and measuring of trabecular thickness with line intercepts technique. Each point overlaying bone (A) or bone marrow (B) is counted, resulting in bone- and marrow volume fractions. Each time a line intercepts a bone surface (C) it is counted. Together with the counted bone volume, the bone intercepts is used to approximate the trabecular thickness.

Fig. 4a
Section of Calcibon specimen with ROI 1marked – the cement macroscopically visible

Fig. 4b
Delineation of the cement-bone interface with the software – crevices were crossed since only tissue covered surfaces were counted

Fig. 4c
Counting of covering of the cement surface with the line intercept technique. (A) marks a cement-bone intercept, and (B) marks a cement-Fibrous tissue intercept. From this, fractions of tissue covered cement can be approximated

Fig. 5a
Bone on growth on the cement surface

Fig. 5b
Dense fibrous covering of cement surface

Tables

Table 1

Patient material and inclusion criteria's

Patient material:	Patients planned for open-wedge HTO, November 2004 – June 2006
Inclusion criteria's:	Medial arthrosis, Ahlbäck gr. 1-2 Signed informed content
Exclusion criteria's:	Age > 18 years or < 65 years Medication with corticosteroids/NSAID BMI > 35 Previous surgery in lateral knee compartment Arthritis secondary to fracture Lack of informed content

Table 2

Patient characteristics

	All	**Local bone autograft**	**Iliac crest autograft**	**Calcibon**
	n = 36	**n = 13**	**n = 12**	**n = 11**
Sex (Women/men)	Women n = 7 Men n = 29	Women n = 3 Men n = 10	Women n = 3 Men n = 9	Women n = 1 Men n = 10
Age mean (years)	49.8	52.9	48.5	47.5
SD	7.4	5.5	9.8	5.4
Smokers	11/36	6/13	2/12	3/13
BMI mean	27.8	27.6	27.3	28.4
SD	3.6	3.4	4.6	2.6
Gap size (mm)	10.1	10.8	8.5	11.1
Range	5 - 17.5	6.25 -17.5	5 - 15	6.25 - 15
Time to hardware removal Mean (months)	13.3	12.7	13.8	13.5
SD	1.5	0.9	2.2	1.1

Table 3

Surface fractions - ICPC

Case Number	Bone covered Fraction	Fibrous covered Fraction	Demarcation of ICPC
1	100	0	No
2	100	0	No
3	100	0	No
4	98	2	No
5	69	31	Yes
6	45	55	Yes
7	40	60	No
8	39	61	No
9	39	61	No
10	19	81	Yes
11	5	95	Yes
N	11	11	
Median	45	55	
Max	100,00	95	
Min.	5	0	

Table 4

BV/TV and trabecular thickness – bone autograft groups – ROI II = osteotomy gap

	Local graft (N = 13)		Iliac crest graft (N = 12)				
	Mean	SD	Mean	SD	Mean diff.	95 % CI	p-value
ROI II, "Defect"							
BV/TV (%)	24.1	12.7	27.7	9.5	3.5	-5.8 -12.9	0.443
Trabecular thickness (µm)	114	58	97	40	17	- 24 - 60	0.400

Table 5

BV/TV and Trabecular thickness – ROI I = "Original trabecular bone"

ROI I - "Original trabecular bone"		N	Mean	SD	95 % CI	
					Lower Bound	Upper Bound
BV/TV (%)	**Control**	13	29.1	14.1	20.6	37.6
	Cristagraft	12	24.6	8.2	19.4	29.8
	Calcibon	11	34.9	10.0	28.2	41.7
Trabecular Thickness (µm)	**Control**	13	132	61	95	169
	Cristagraft	12	127	29	96	158
	Calcibon	11	159	60	119	199

Figures

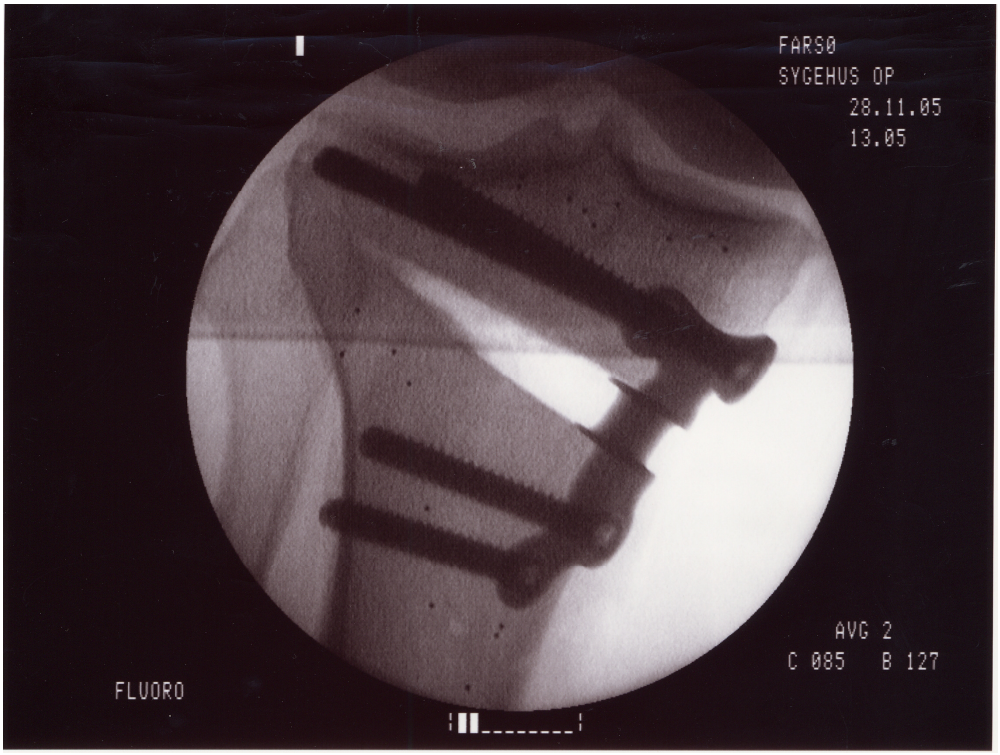

Fig. 1a

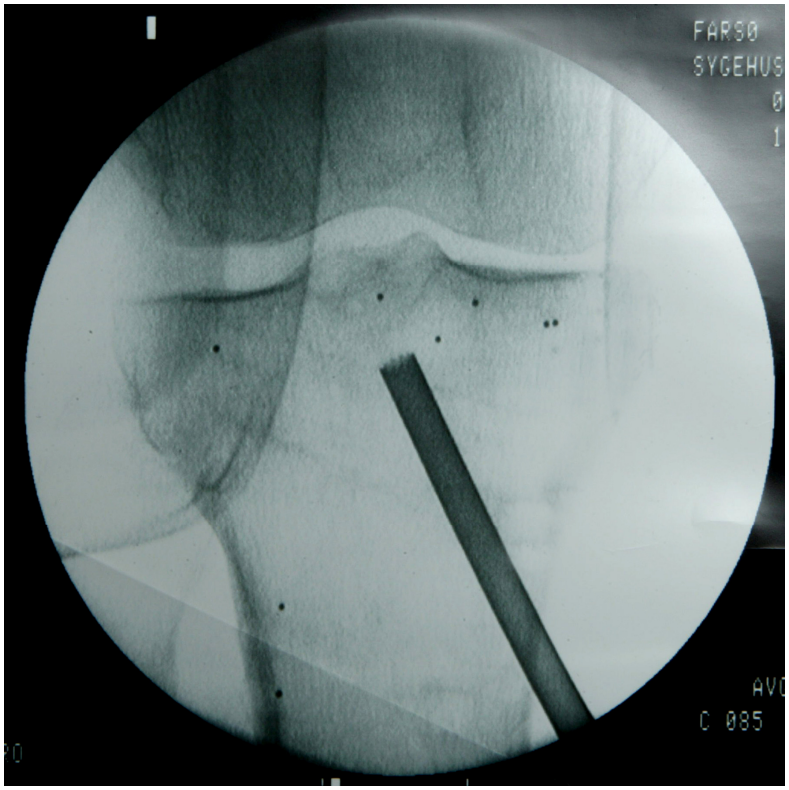

Fig. 1b

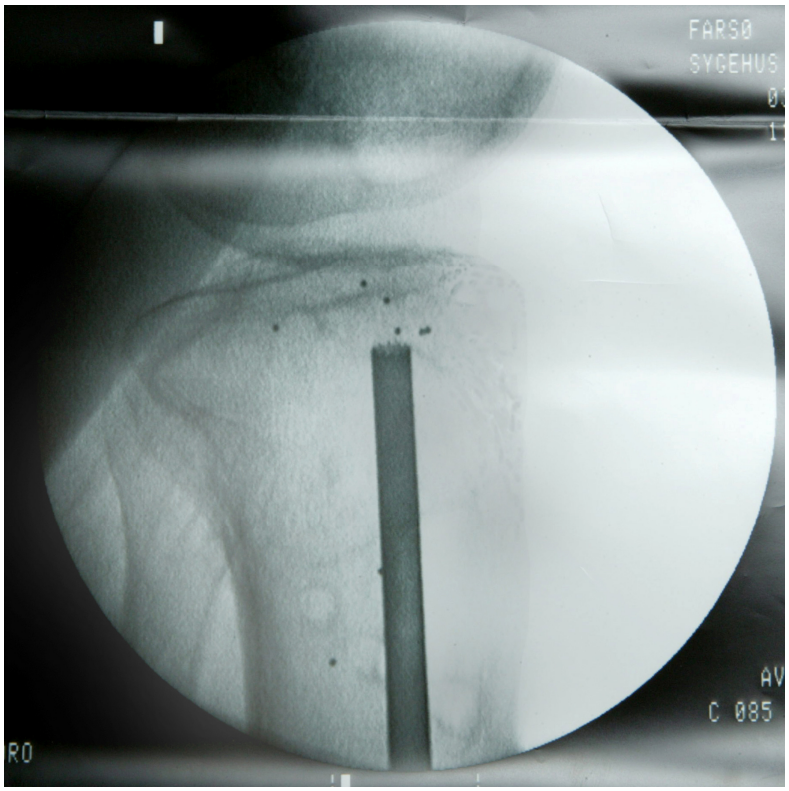

Fig. 1c

Fig. 2a

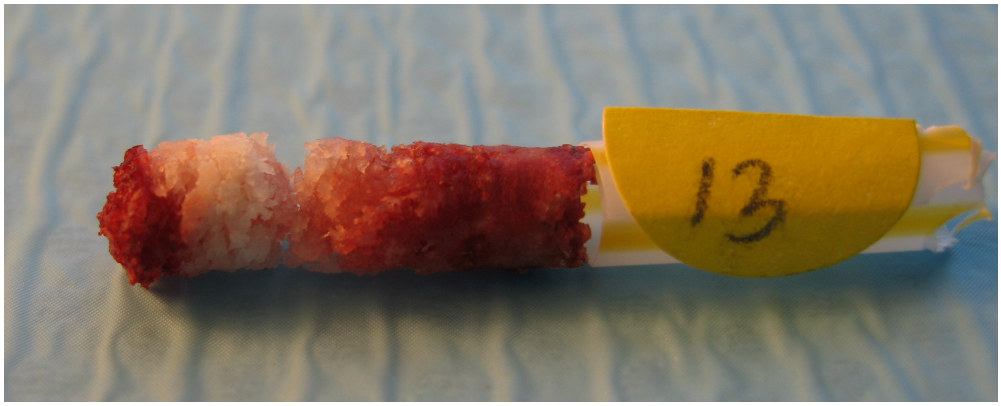

Fig. 2b

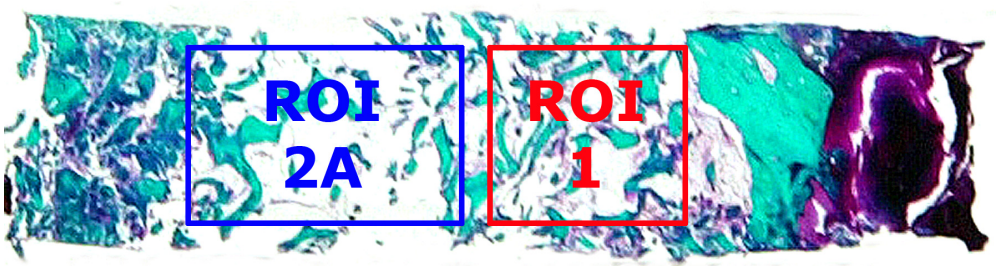

Fig. 3a

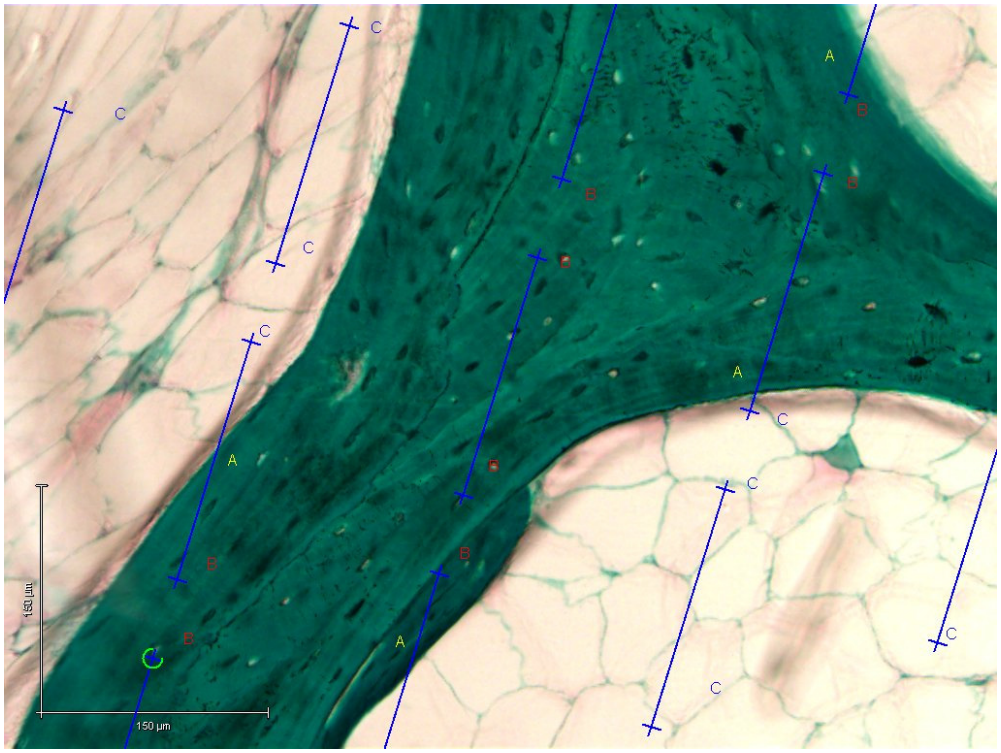

Fig. 3b

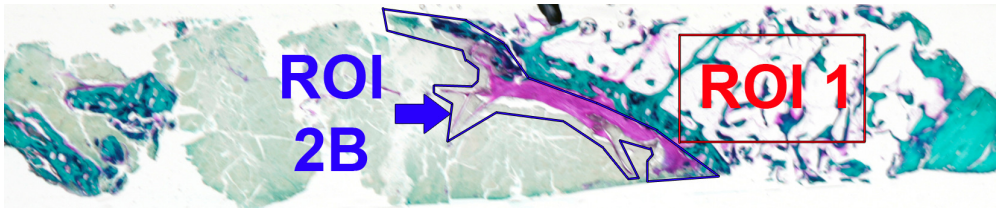

Fig. 4a

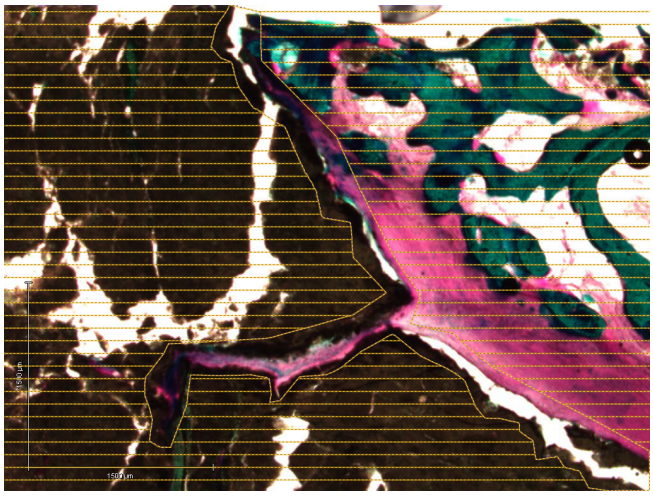

Fig. 4b

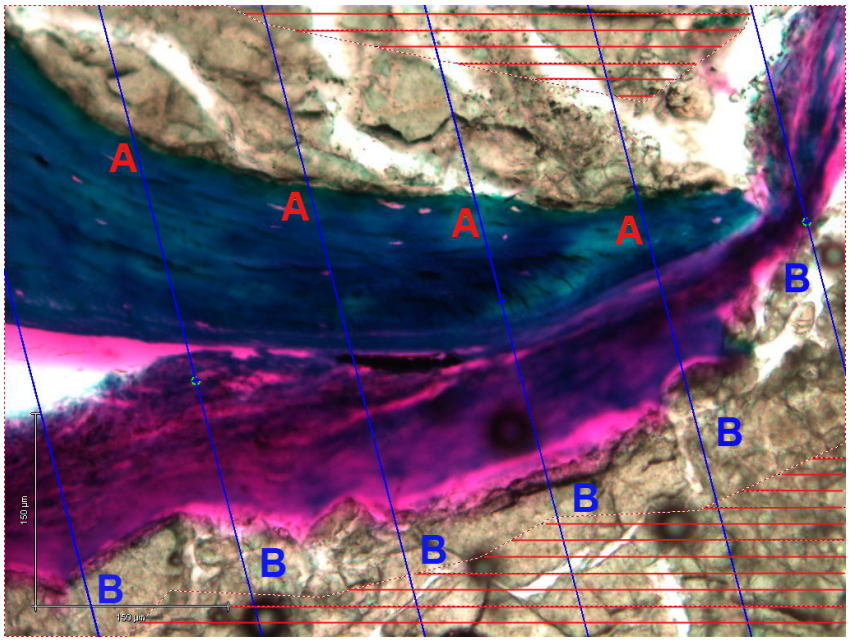

Fig. 4c

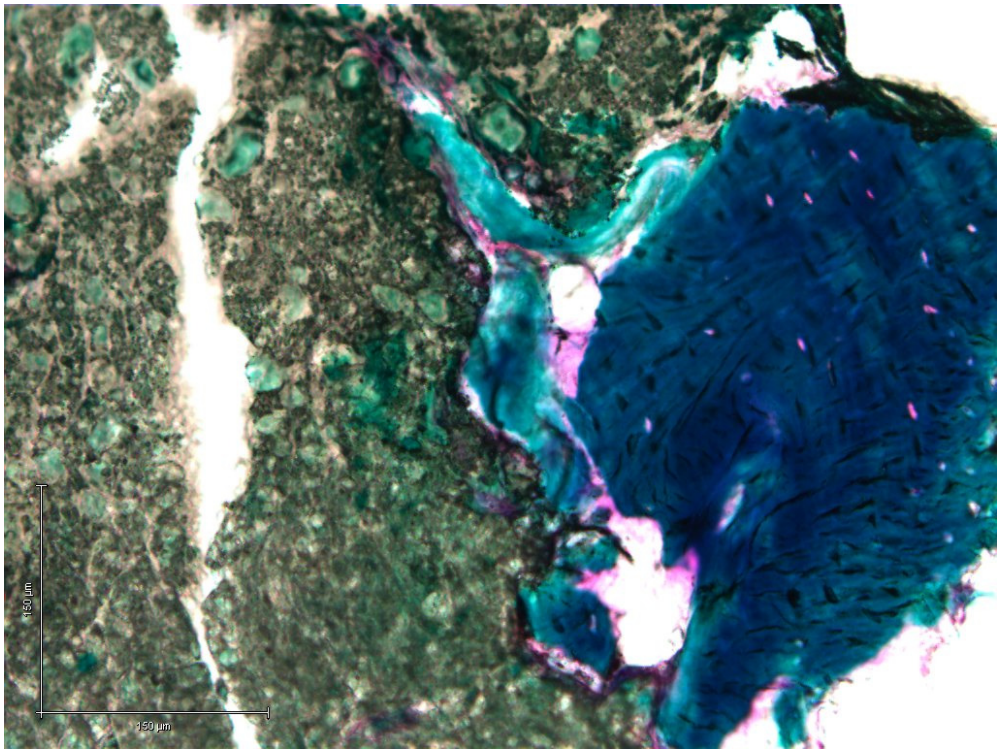

Fig. 5a

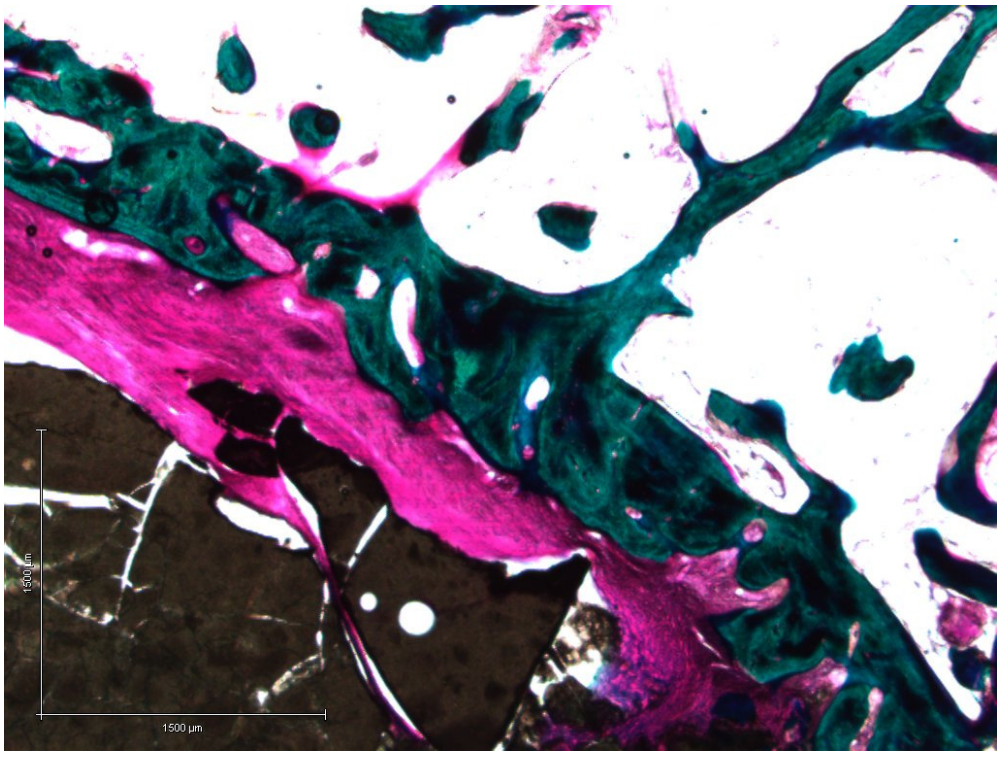

Fig. 5b