Can donor site morbidity in children be eradicated?

- Is donor bone graft equally efficient as patient bone graft in flat foot surgery in children?

Resume

Patient bone graft harvested from the iliac crest has for many years been the gold standard in paediatric orthopaedics. However, donor site morbidity such as chronic pain, disturbed sensibility and infection has led surgeons to investigate alternatives, for example artificial bone grafts or bone grafts from donors. While some centers have good experience with donor bone grafts, the scientific evidence regarding its efficacy and safety compared with autograft is scarce. The main aim of this project is to proof, that donor bone graft is equally efficient as patient bone graft in flat foot surgery of children. With the established Iliac Crest Allograft Biobank at Aarhus University Hospital, we want to evaluate the efficacy of donor bone graft in paediatric orthopaedic surgery. The project consist of the following studies. First, a **systematic review** of the existing literature evaluating the efficacy of patient and donor bone grafts in children. Secondly, a **retrospective case series** evaluating clinical outcome of paediatric patients surgically treated for flatfeet with donor bone grafts in the period 2010-2019 in Münster, Germany. Thirdly, the main study: a **multicentre, randomized, controlled non-inferiority trial** comparing the use of donor bone graft vs patient bone graft in paediatric flat foot surgery using established and validated methods from a previous PhD project with a sample size of 30 patients in each group. Primary outcome is going to be radiological stability and secondary outcome a validated patient reported outcome measure. This project will be a part of an already established collaboration between the Department of Orthopaedics at Aarhus University Hospital, Aalborg University Hospital in Denmark and University Hospital of Münster, Germany.

We hope that donor bone graft proves to be non-inferior to patient bone graft. If this holds true, bone harvesting from the patient is no longer needed and the project thus holds the potential to eradicate acute and chronic donor site pain and morbidity, which up to 30% of children suffer from.

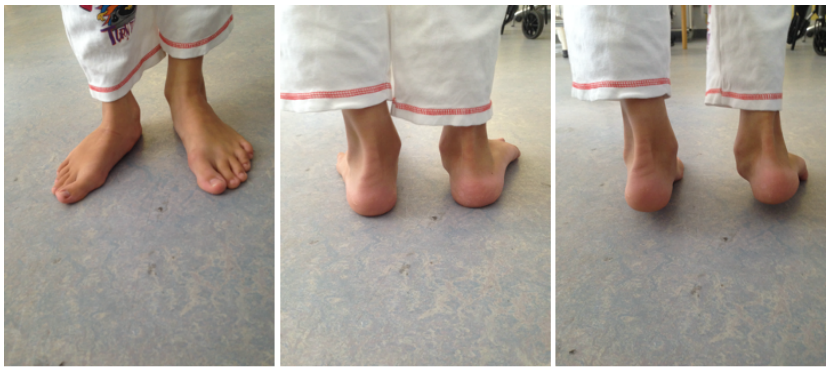
Aim

The main aim of this project is to eradicate acute and chronic donor site pain and morbidity, which up to 30% of children suffer from after bone grafting from the iliac crest (1). Moreover, this will decrease surgery time and potentially length of hospital admission. The Tricortical Iliac Crest Allograft Biobank at AUH is the first of its kind in the Nordic countries and puts this aim within reach.

Hypothesis

The main hypothesis is, that donor bone graft is radiological and clinical non-inferior to patient bone graft in paediatric orthopaedic surgery. This hypothesis has to be investigated scientifically for each clinical application. This project will test this thesis in surgical treatment of flatfeet.

Background



Clinical photo of a flatfoot. Midfoot abduction (left), hindfoot valgus with "too many toes" sign (middle). In double-heel rise the hindfoot valgus converts into varus apperance in the flexible hindfoot (right).

Flat foot is a frequent clinical presentation in the paediatric orthopaedic outpatient clinic (2). Most often the condition is physiological, e.g. flexible, painless and with no functional compromise and normally disappears at the age of 8-10 years (2). However, non-physiological flatfeet is typically associated with pain localised under the talar head during weight bearing. If left untreated, there is a risk of impairment of normal gait development. Conservative treatment includes physiotherapy, shoe wear modifications and orthotics. When conservative treatment fails and the patients are limited within their daily lives due to foot pain, surgery may be the only option. Evan's calcaneal lengthening osteotomy is the most common surgery for this foot deformity (3). The surgical procedure corrects the paediatric flat foot without interfering with the calcaneal growth plates or scarifying the subtalar joint mobility. The concept of this procedure is to lengthen the calcaneus by insertion of a trapezoidal-shaped bone graft, thereby correcting the deformity. The valgus is reduced, the supinated forefoot is pronated and the medial longitudinal arch is restored. The bone graft used is routinely harvested from the iliac crest (4,5).

Clinical Problem

Patient bone graft, that is bone harvested from the iliac crest of the patient, is needed in several paediatric orthopaedic surgeries, for example in management of flat foot and hip dysplasia. Patient bone graft is the current gold standard because of its structural stability and bone forming capacity (6,7,8). However, almost one third of patients suffer from complications at the harvesting site. Postoperative haematoma, changed sensation due to nerve damage as well as superficial and deep infection have been reported (1).

Moreover, chronic pain from the harvesting site is reported by 27 % of the patients after two years and acute postsurgical pain from the harvesting site is often worse than the pain from the primary surgical site (9,10).

In a retrospective study with a minimum follow up of 2 years, 21 of 87 children (24%) reported pain at the harvest site and 15% reported problems severe enough to interfere with daily activities. The self-reported pain ranged from 1-10 with a mean of 4 (11).

This has led surgeons and researchers to investigate alternatives to autologous bone graft.

Solution

A retrospective study describes donor bone graft as a potential alternative in children with no major complications and all cases had bony union and satisfactory results at the final exam (12).

Some groups report good short results after the use of allografts in calcaneal lengthenings, but the scientific evidence is sparse (12-17). To the best of our knowledge no randomized controlled trials (RCT) have compared donor bone graft vs. patient bone graft in children. Frozen donor bone graft does not contain living cells and therefore lacks osteoinductive capacity. However, it is osteoconductive and paediatric patients have a high bone healing potential (18). It seems thus clinically reasonable to test the hypothesis, that donor bone graft is non-inferior compared with patient bone graft in children undergoing flat foot surgery.

The approved Tricortical Iliac Crest Allograft Biobank, AUH puts us in the unique position to perform a multicentre, randomized, controlled non-inferiority trial. If donor bone graft proves to be non-inferior to patient bone graft, it is likely to become the new gold standard in Children's Orthopaedics. Without the need for bone harvesting from the patient, acute and chronic donor site pain would thus be eradicated.

Furthermore, the surgery time would decrease and the duration of hospital admission would potentially be shortened.

Methods

The main aim is to evaluate the efficacy of donor bone graft in paediatric patients undergoing flat foot surgery. Our hypothesis is that donor bone graft is non-inferior to patient bone graft in Evan's calcaneal lengthenings in terms of radiographic and clinical outcomes and superior in terms of complications from the harvesting site. Its methods are based on a previous PhD-project from our group by Polina Martinkevich comparing patient bone graft with artificial grafts (19-22). This study was stopped at an interim analysis due to impairment of the structural stability of the artificial graft. Donor bone graft on the other hand has sufficient structural stability.

Study 1 (EPOS financed):

Allogenous vs. autogenous bone grafts in paediatric foot surgery: A systematic review

A systematic review of the existing literature evaluating the efficacy of patient bone graft vs. donor bone grafts in paediatric orthopaedic surgery and secondary to provide information about the associated complications. The study will adhere to the PRISMA-P guidelines and will be registered in the Prospero database.

Study 2 (EPOS financed)*:*

The use of allogenous bone grafting in 35 paediatric flatfoot patients. A retrospective case series.

A retrospective case series evaluating the clinical outcome of 35 paediatric patients withsurgical flat foot treatment at University Hospital of Münster, Germany in the period 2010-2019. Patients will be identified

using ICD-10 codes for bone transplantation and flat foot. Data will be extracted electronical patient journals and radiographs.

Primary outcome:

Complications (reoperation, non-union, graft collapse and infection).

Secondary outcome:

AOFAS Ankle Hindfoot Scale, PROMs (Oxford Ankle Foot Questionnaire, European Quality of Life (EQ5D), Short Form 36 Health Survey (SF36), Radiographs (Lateral talo-1st-metatarsal angle (TMA), lateral calcaneal pitch angle (CP) and lateral talocalcaneal angle (TCA)), plantar pressure distribution measurement and perioperative parameters (Duration of surgery, x-ray duration and dose, duration of hospital admission).

In 2022, all patients will be offered new clinical and radiographic examinations, and their functional outcome and quality of life will be assessed with PROMs.

Study 3 (additional funding required)*:*

Multi-center randomized controlled trial comparing iliac crest autograft vs allograft for calcaneal lengthenings in a paediatric population (AUH, AaUH, UKM)

The study will be registered at clinicaltrials.gov and adhere to CONSORT guidelines. Research Electronic Data Capture (REDCap) and its randomization module will be applied for randomization and data collection.

The calcaneus lengthening osteotomy will follow the standard procedure at the institution. In preparation of radiostereometric analysis (RSA), the distal and proximal fragment of the calcaneus will be marked with tantalum beads.

Inclusion:

Patients with symptomatic flexible flatfoot scheduled for calcaneus lengthening osteotomy at AUH, AaUH and UKM will be considered eligible for inclusion if they meet the following criteria: Age 5 to 16 years, no major cognitive impairments, ability to walk independently, no other planned ipsilateral orthopaedic operations.

Statistics:

Sample size calculations followed the non-inferiority continuous outcome trial method developed by Sealed Envelope Ltd 2012 (23). Non-inferiority of the donor bone graft will be claimed if the upper limit of a one-sided 95% confidence interval with a significance level of 5%, a power of 90%, a standard deviation of 1.5 mm will be below a predefined non-inferiority limit of 2 mm x-translation ((+) x-translation: osteotomy ’compression’ and (-) x-translation: osteotomy ’distraction’.). This will require a sample size of 26 patients in each group. To ensure enough data in case of drop-out, cross-over, 30 patients will be enrolled. The non-inferiority limit is based on the PhD project by Martinkevich, 2016 as well as the clinical experience (19,20).

Intention to treat and treated per protocol analyses will be performed.

Primary outcomes:

Radiologic stability of the graft assessed with RSA 2-3 days after surgery as baseline and after 1.5, 3, 6 and 12 months.

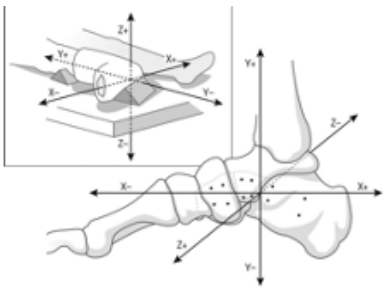
Secondary outcomes:

Pain (Patient and caregiver reported), radiographs (TMA, CP, TCA), AOFAS Ankle Hindfoot Scale, PROMs (Oxford Ankle Foot Questionaire, European Quality of Life (EQ5D), Short Form 36 Health Survey (SF36)), plantar pressure distribution measurement, perioperative parameters (Duration of surgery, x-ray duration and dose, duration of hospital admission) and complications (chronic pain, dysesthesia n. cutaneous femoris lateralis, superficial and deep infection, reoperation, cosmetic (hypertrophic scarring (photo documentation incl. ruler)).

Outcomes

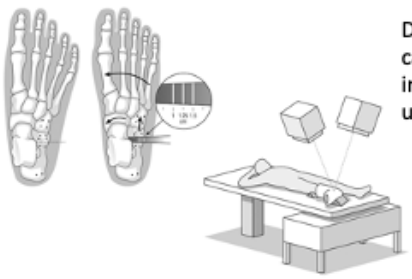
RSA:

Radiostereometric analysis is a well-accepted method for assessment of in vivo three dimensional motion between bony structures. Marker-based RSA with insertion of spherical tantalum beads into the region of interest creates well-defined measurement point which enable accurate measurements of migration from RSA radiographs. The marker models in the coordinate systems is oriented with the osteotomy performed in the y-axis, the lengthening in the x-axis, and any medial lateral movement of the migration object with reference to the rigid object would occur in the z-axis. A distraction of the osteotomy would be indicated by a negative sign in the x-translations and, conversely, a positive sign in the x-translations would indicate compression of the osteotomy. We have previously established the method's feasibility, precision and repeatability (19-21).



RSA

Drawing illustrating the orientation of the coordinate system relative to the anatomy of the foot. The foot is viewed from the medial side, with the dotted lines representing the contour of the distal part of both the calcaneal bone and the cuboid bone.



Drawing showing the principles in a lateral calcaneal lengthening osteotomy with inserted tantalum markers (left) and the set-up of the radiostereometric analysis (right).

Conventional radiographs:

The lateral talo-1st-metatarsal angle (TMA) is formed between the long axis of the talus and first metatarsal on a weight-bearing lateral view and is used as a measurement of collapse of the longitudinal arch.

The lateral calcaneal pitch angle (CP) is drawn on a weight-bearing lateral foot radiograph between the inclination axis and the horizontal surface and reflects the height of the foot framework. The lateral talocalcaneal angle (TCA) is also drawn on a lateral weight bearing view to evaluate hindfoot valgus. All of the above to evaluate graft-incorporation and healing.

Clinical outcomes:

AOFAS:

The AOFAS Ankle-Hindfoot Scale consists of a patient-reported and physician reported scale with focus on pain, function and alignment.

Oxford Ankle Foot Questionaire:

This Is a region-specific health-related PROM consisting of 14 questions. It covers three domains as experienced by the child and his/her parents during the previous week: physical activity, school and play, emotional and an item relating to footwear with four possible answers for each item. This was translated to danish and validated in a previous study by Martinkevich et al.

European Quality of Life (EQ5D) (youth edition):

EQ5D comprises 5 dimensions; mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy and each dimension has 3 levels: no problems, some problems and a lot of problems.

Short Form 36 Health Survey (SF36):

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. The sections are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

Wong Baker Scale:

The patient chooses the face that best illustrates the physical pain they are feeling.

Revised Faces Pain Scale (FPS-r):

Self-reported measurement of pain intensity developed for children.

Plantar Pressure distribution measurement:

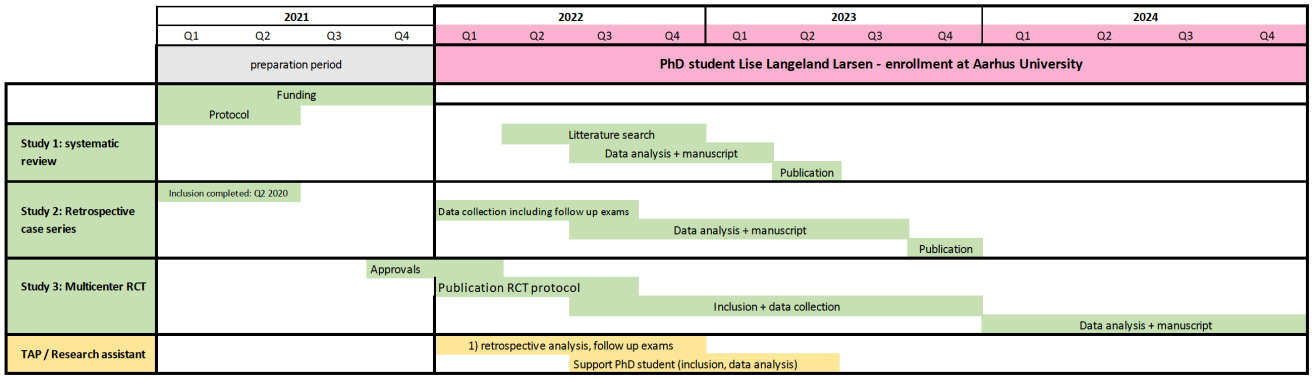
Standardized and well-established protocol by Pedersen LK using HR Mat™ (Tekscan® Inc. South Boston, MA, USA).

Feasibility

This PhD-project has already been approved for enrollment at the Graduate School of Health, Aarhus University and the offer is valid until 1 June 2022 provided funding of the entire project is obtained.

Collaboration between the Department of Orthopaedics from AUH, AaUH and UKM is already established and several mutual publications have been published. The primary outcome of the RCT, i.e. RSA measurement, has previously proved to be feasible to evaluate calcaneal lengthening osteotomies at our institution (19-22). All necessary permits and funding for the establishment of the Tricortical Iliac Crista Allograft Biobank, AUH have been obtained. The Biobank was established in September 2020 and is ready for scientific and clinical use. This project is within the timeline of a PhD-project, please refer to our Gantt schedule.

Scientific activities and milestones (inclusion completed, data collection completed, publication)



Funding

Currently we are awaiting applications for the Novo Nordisk Foundation (2.105.400 DKK) and Gangsted Foundation (420.500 DKK).

We hope to be considered for funding from the EPOS foundation. An acknowledgement from EPOS in particular will mean a lot to us and this project. A grant from the EPOS foundation will cover salary for a shorter period prior to our planned enrollment and give the opportunity to our future PhD student (1) to conduct the systematic review and (2) to perform the retrospective study as well as (3) apply for additional funding for the RCT.

Ethics

Ethical approval is pending, however it has previously been granted for a RCT applying the same outcome measures. The previous approved RCT and its patient information will be used as templates for the application for ethical approval. Informed consent will be obtained from all patients / legal guardians. All studies will be performed in accordance with the Declaration of Helsinki. This project cannot successfully be carried out using adult patients, since the diagnosis is specific for children of growth age. Inclusion can directly benefit the

participating child, since there is no need of bone harvesting, why they will be sparred possible complications from the harvest site. The project carries minimal risks and harms for the child.

Patients that match the inclusion criteria will, at the preliminary exam with their parents/legal guardians, be informed by the doctor, who will perform the surgery. This surgeon will be an orthopedic surgeon with children's orthopedics as specialty. Oral information will therefore be presented by a person with the necessary pedagogical competences. Materials in writing explaining the project will be handed out including the folder "Forsøgspersonernes rettigheder i et sundhedsvidenskabeligt forskningsprojekt". The child and parents will be informed of the possibility of an extra exam prior to surgery with Associate Professor Jan Duedal Rölfing, in case of doubt or any questions. There will be a reflection time of 4 weeks and hereafter consent. Deputy consent from both custodians. The patients physical and mental health will be taken into consideration and respected.

Publishing and dissemination of results

We aim to publish the protocol of the RCT study in BMC Musculoskeletal Disorders (impact factor: 2.050) prior to the study in order to ensure transparency. Public information is going to be disseminated through dpor.dk, social media and the public relations departments of AUH and UKM.

Collaboration

The Principal Investigator is Associate Professor Jan Duedal Rölfing, AUH. This project will be carried out in collaboration with PhD student, MD Lise Langeland Larsen responsible for inclusion of patients and data management. Site managers are going to be Prof. Bjarne Møller-Madsen, AUH (h-index: 27), Prof. Robert Rödl, UKM (h-index: 23) and Prof. Ole Rahbek, Aalborg University Hospital (AaUH, h-index: 21).

University Hospital of Münster: Department of Children's Orthopaedics, Deformity Reconstruction:

Professor Robert Rödl, Dr.med. Björn Vogt. The department is one of the largest Children's Orthopaedic and Deformity Reconstruction Departments in Europe performing annually approximately 500 osteotomies, 250 growth surgeries, 100 limb lengthening surgeries, 100 soft tissue procedures and 200 other foot surgeries. The collaboration resulted in an official invitation of Associate Professor Jan Duedal Rölfing as a Visiting Professor for the initial duration of 4 years, e.g. 1st January 2021 – 31st December 2024, which coincides with the timeline of the first mutual PhD student. Two visits of 4 months duration are planned. The first visit already commenced in June 2021.

Danish Paediatric Orthopaedic Research (dpor.dk), Children's Orthopaedics AUH

DPOR.dk was founded in 2011 and is a collaboration with several international partners. Monthly meetings are scheduled where current research is being discussed. Paediatric orthopaedic surgeons at AUH, AaUH and UKM will be performing the surgeries in our RCT study.

Scientific steering committee of the collaboration:

JDR, BMM, RR, OR and BV. Status meetings will be held 6 times yearly either virtually or physically. Ad hoc meetings resolving arising obstacles and questions will be held as needed. Site investigators being chief responsible for the daily conduction of the RCT studies: JDR at AUH, BV at UKM, OR at AaUH. Any potential issues will be discussed with the steering committee. PhD student will include and follow-up the patients assisted by 3 TAP/student assistants. The PhD student will perform the analyses and write the first drafts of the papers.

Other collaborators:

Daniel Wæver, MD, Dept. of Orthopaedics, Regional Hospital Randers has extensive experience in designing and conducting systematic reviews and metaanalyses and will contribute to our systematic review.

Significance

First and foremost, we hope, that donor bone graft proves to be non-inferior and can thus supersede patient bone graft as gold standard in paediatric orthopaedic surgery. If so, postoperative and chronic pain from the harvesting site will be eradicated. Decreased surgery time and potentially the duration of hospital admission are side effects, which will be evaluated in cost-effectiveness studies. At AUH we have the first Tricortical Iliac Crista Allograft Biobank in the Nordic countries and the opportunity to evaluate its efficacy together with our national and international partners.

After the project period, the donor bone graft from the biobank at AUH will be made available for all Danish Children's Orthopaedic Departments at non-profit cost.

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