AARHUS
UNIVERSITY

Guided growth of long bones using the tension band plating technique

Experimental and clinical studies

PhD thesis

Martin Gottliebsen

Health
Aarhus University
2013

PhD thesis by Martin Gottliebsen
Health, Aarhus University
Public defence: Friday 22 February 2013 at 02.00 p.m.
Lille Anatomisk Auditorium (Lokale 424), Building 1231, Aarhus University

Guided growth of long bones using the tension band plating technique

Experimental and clinical studies

PhD thesis

Martin Gottliebsen

Health
Aarhus University
2013

Supervisors

Bjarne Møller-Madsen MD DMSc Professor
Dept. of Children`s Orthopaedics
Aarhus University Hospital NBG
Nørrebrogade 44, 8000 Aarhus C
Denmark

Ole Rahbek MD PhD Associate Professor
Dept. of Children`s Orthopaedics
Aarhus University Hospital NBG
Nørrebrogade 44, 8000 Aarhus C
Denmark

Evaluation committee

Professor Pierre Lascombes, MD
Orthopedia pediatrique
Centre Hospitalier Universitaire de Genève
Switzerland

Deborah Eastwood, MB, FRCS
Great Ormond Street Hospital, London
United Kingdom

Associate professor Johnny Keller, MD, DMSc (chairman of the committee)
Department of Orthopaedics, Aarhus University Hospital
Denmark

Preface

This thesis is based on experimental and clinical research conducted at Orthopaedic Research Laboratory at Aarhus University Hospital, Denmark, Department of Animal Health and Bioscience, Foulum, Aarhus University, Denmark and Department of Children`s Orthopaedics, Aarhus University Hospital from September 2008 till August 2012. My research has kindly been supported by grants from The Danish Rheumatism Association, Clinical Institute at Aarhus University, The Central Denmark Region, The AP Moller Foundation and The Guildal Foundation.

I would like to offer my sincere thanks to Bjarne Møller-Madsen for being my supervisor throughout this process as a PhD student. Both as a researcher and orthopaedic surgeon you have been a great inspiration. I am grateful for your faith in my work and for constantly encouraging me to seek answers to new questions.

I owe a great deal to Ole Rahbek for introducing me to orthopaedic research and for fostering interesting ideas suited for studies. You have been a rock solid support always providing constructive feedback and motivating me to overcome obstacles and challenges in daily work.

Many thanks are also due to;
-Arne Bach and Maj Friis Jespersen, Hospital Unit West
-Michel Bach Hellfritzch Department of Radiology, AUH
-Juan and Line, my fellow PhD students
-Hans Stødkilde-Jørgensen, MR research centre, AU
-Ivan Hvid and Michael Davidsen, Department of Children`s Orthopaedics, AUH
-Hanne Damgaard Poulsen, Research Centre Foulum, AU
-Manoj Ramachandran, The Royal London Hospital.

Furthermore I am very thankful to all the staff and colleagues at the Orthopaedic Research Lab for helping with fixation of tissue, preparation of samples, analysis and also very important all the discussions between research groups that has given me inspiration for new studies.

I owe everything to my family; my parents, Kristian, Agnete, Tor, Mia and Laila. My love Laila has always believed in me and backed me up in my decisions that has not always been easy to stand up to. Your invaluable help with my experiments is also highly appreciated.

Martin Gottliebsen
Silkeborg, February 2013

The thesis is based on the following papers:

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

I. Gottliebsen M, Rahbek O, Damgaard Poulsen H, Møller-Madsen B. Similar growth plate morphology in stapling and tension band plating hemiepiphysiodesis. A porcine experimental histomorphometric study. *J Orthop Res. 2012 Nov 28. doi: 10.1002/jor.22276. [Epub ahead of print]* *

II. Gottliebsen M, Møller-Madsen B, Stødkilde-Jørgensen H, Rahbek O. Controlled longitudinal bone growth. An experimental study. *Accepted for publication in The Bone & Joint Journal.* **

III. Gottliebsen M, Rahbek O, Hvid I, Davidsen M, Hellfritzch MB, Møller-Madsen B. Hemiephysiodesis: similar treatment time for tension-band plating and for stapling. A randomized clinical trial on guided growth for idiopathic genu valgum. *Accepted for publication in Acta Orthopaedica* ***

* Presented at The Annual Meeting for The Danish Orthopaedic Society, Copenhagen, 2011, at The 31st Annual Meeting of the European Paediatric Orthopaedic Society, Helsinki, Finland, April 2012 and at The 13th EFORT meeting, Berlin, Germany, May 2012

** Presented at The Annual Meeting for The Danish Orthopaedic Society, Copenhagen, 2011, at The 31st Annual Meeting of the European Paediatric Orthopaedic Society, Helsinki, Finland, April 2012 and at The 13th EFORT meeting, Berlin, Germany, May 2012

*** Presented at The Annual Meeting for The Danish Orthopaedic Society, Copenhagen, 2012 and selected for podium presentation at The 32nd Annual Meeting of the European Paediatric Orthopaedic Society, Athens, Greece, April 2013

Awards:
(I) was highlighted for Basic Science prize competition at The 31st Annual Meeting of the European Paediatric Orthopaedic Society, Helsinki, Finland, April 2012
(II) was awarded the Best Basic Science Paper Award at The 31st Annual Meeting of the European Paediatric Orthopaedic Society, Helsinki, Finland April 2012

Abbreviations

ACL; anterior cruciate ligament

AUH; Aarhus University Hospital

CHQ; Child Health Questionnaire

CTEV; congenital talipes equino varus

DDH; developmental dysplasia of the hip

HE; haematoxylin eosin

IGV; idiopathic genu valgum

LDFA; lateral distal femoral angle

LLD; leg length discrepancy

MAD; mechanical axis deviation

MMA; methyl methacrylate

MPTA; medial proximal tibial angle

MRI; magnetic resonance imaging

OxFAQ; Oxford score of foot and ankle questionnaire

PACS; picture archiving and communication system

POSNA; Paediatric Orthopaedic Society of North America

PRO; patient reported outcome

RCT; randomized controlled trial

ROI; region of interest

VAS; visual analog score

Contents

English summary 1
Danish summary 2
Introduction 4
    General background 4
    Biology of skeletal growth 4
    Angulating deformities and leg length discrepancy in growing children 5
    Manipulation of skeletal growth 6
    Methods and techniques for guiding growth in bones 7
    Tension band plating 9
Aim of the thesis 12
Materials and methods 13
    Hypotheses 13
    Study designs 13
    Animal model 15
    Patients in the clinical study 16
    Ethics 17
    Histomorphometry (I) 17
    Magnetic Resonance Imaging (II) 18
    Radiographic imaging (III) 21
    Clinical parameters (III) 21
    Statistical considerations 22
Summary of Results 25
    Paper I: 25
    Paper II: 27
    Paper III: 29
Discussion 34
Conclusions 39
Perspectives and future research 40
References 41
Appendices 53
Papers I-III 55

English summary

Controlled growth of bones using different closed and surgical techniques can be used as treatment in a number of conditions in paediatric orthopaedics. The growing skeleton is susceptible to manipulation of the growth plate and by doing this it may be possible to avoid more extensive surgical procedures. With leg length discrepancy (LLD) a timed epiphysiodesis (closure of a growth plate) on the longest leg can be used as treatment in milder cases. Commonly today a permanent technique with closure of the growth plate is being used. This necessitates timing of the procedure to ensure equalisation of the legs at skeletal maturity. Performing a temporary closure of the growth plate is appealing as intervention then can be performed at an earlier stage. Unilateral epiphysiodesis (or hemiepiphysiodesis) can be used to correct angulating deformities. Traditionally staples have been used to perform a reversible hemiepiphysiodesis. During the last decade a new principle called tension band plating using a small extra periosteal plate and two screws has gained popularity. Tension band plating has been described to have a theoretical advantage compared to stapling. Several clinical and experimental studies has investigated the use of tension band plating but it still remains unclear if the tension band plating technique has a more biological effect on the growth plate than stapling.

The aim of the thesis was to investigate the use of tension band plating in relation to angulating deformities and LLD.

In Paper I growth plate morphology was compared after tension band plating and stapling in an animal experimental study. Both the immediate response and the delayed response after hemiepiphysiodesis were studied using quantitative histomorphometry. The ability to perform a temporary epiphysiodesis using tension band plating in a similar animal model was investigated in Paper II. In this study the animals were followed with magnetic resonance imaging. The outcome was changes in interphyseal distance and metaphyseal water content. Finally in Paper III, stapling and tension band plating was compared in a randomized clinical study in children with idiopathic genu valgum. Treatment time as well as changes in intermalleolar distance and radiographic parameters was evaluated.

The results showed similar changes in growth plate morphology between stapling and tension band plating in Paper I. The delayed response to hemiepiphysiodesis appears to be growth plate enlargement and disorganisation of cartilage tissue (Paper I). It was possible to induce a temporary growth control in the animal model in paper II with a shortening of the treated bone. Furthermore, changes in metaphyseal water content were correlated with bone growth. In Paper III no differences were found between stapling and tension band plating in relation to treatment time, intermalleolar distances, and measured radiographic values on long standing x-rays.

In conclusion, the theoretical advantage of tension band plating towards stapling is probably of minor importance in clinical practice. Temporary epiphysiodesis using tension band plating may have a role in treatment of LLD, but future clinical studies are needed to investigate this.

Danish summary

Kontrol af knoglevækst med forskellige lukkede og åbne teknikker benyttes hyppigt indenfor en række tilstande ved børneortopædien. Mens barnets skelet vokser kan vækstzonen i knoglerne manipuleres, og på den måde kan det være muligt at undgå mere omfattende kirurgiske indgreb. I forhold til behandling af mildere tilfælde af benlængdeforskel hos børn kan en planlagt epifysiodese (lukning af en vækstzone) i det længste ben benyttes som behandling. Almindeligvis vil lukning af en vækstzone i dag blive foretaget med en permanent teknik. Dette medfører at indgrebet skal planlægges, således at barnet opnår lige lange ben når det er udvokset. Mulighed for at udføre en midlertidig lukning af vækstzonen har indlysende fordele, da det vil være muligt at foretage udligning af benlængdeforskel på et tidligere stadie. Halvsidig lukning af vækstzonen (hemiepifysiodese) kan benyttes til at behandle vinklende deformiteter i underekstremiterne hos børn. Tidligere har man benyttet kramper til at foretage reversibel hemiepifysiodese, men indenfor det seneste årti har et nyt princip kaldet "tension band plating" vundet indpas i klinikken. Princippet består af en lille skinne og to skruer der placeres over vækstzonen. "Tension band plating" beskrives at have teoretiske fordele overfor krampe behandling. Adskillige kliniske og eksperimentelle studier har undersøgt teknikken, men det er stadig uklart om "tension band plating" har en mere biologisk effekt på vækstzonen end kramper.

Formålet med afhandlingen var at undersøge brugen af "tension band plating" i forhold til korrektion af vinklende deformiteter og benlængdeforskel.

I studie I blev vækstzone morfologi sammenlignet efter krampe og "tension band plating" behandling i en dyremodel. Både den umiddelbare effekt og det forsinkede respons til hemiepifysiodese blev undersøgt ved hjælp af kvantitativ histomorfometri. I en lignende dyremodel blev muligheden for at foretage temporær epifysiodese ved hjælp af "tension band plating" teknikken undersøgt i studie II. Dyrene blev fulgt med magnetisk resonans scanninger, og ændringer i afstanden mellem vækstzoner samt vandindhold i metafysær knogle blev undersøgt. Afslutningsvis blev kramper og "tension band plating" sammenlignet i et randomiseret klinisk studie i børn med behandlingskrævende idiopatisk genu valgum (studie III). Behandlingstid samt ændringer i intermalleolær afstand og radiografiske parametre blev evalueret.

Resultaterne viste ens ændringer i vækstzone morfologi mellem kramper og "tension band plating" i studie I. Det forsinkede respons til hemiepifysiodese forekommer at være fortykkelse af vækstzonen og fravær af vanlig cellulær organisering heri. Det var muligt at foretage temporær epifysiodese i dyremodellen i studie II med forkortning af den behandlede knogle. Ydermere forekommer ændringer i metafysært vandindhold at være korreleret til knogle vækst. I studie 3 fandtes ingen forskel mellem kramper og "tension band plating" i relation til behandlingstid, intermalleolær afstande og vinkler på hofte-knæ-ankel røntgen optagelser.

Det konkluderes at de teoretiske fordele ved "tension band plating" sandsynligvis er af mindre betydning for klinisk praksis. Temporær epifysiodese med "tension band

plating" teknikken kan være en mulighed til udligning af benlængdeforskelle, men yderligere kliniske studier er nødvendige for at undersøge dette.

Introduction

GUIDED GROWTH
The use of closed or surgical manipulation of growing bones to correct deformities and in some cases circumventing the need for open procedures and osteotomies.

General background

The term "Guided Growth" was introduced by Stevens in his papers on the use of hemiepiphysiodesis with tension band plating technique to correct deformities in growing children (1, 2). Manipulation of the growing bone is however an old concept that extends back to the origin of orthopaedics. Andry published his book on prevention of deformities in children in Paris in 1741 (3). It gave instructions to parents to prevent and correct deformities in children. The title of the book included the new term *orthopédie,* synthesized from the two Greek words; orthos (being straight meaning free from deformity) and pais (child). Two years later the book was translated into English with *orthopédie* being translated into *orthopaedia*. The books illustration with a splinted tree is today the icon of the orthopaedic speciality.
The concept of guided growth has gained increasing interest in paediatric orthopaedics recently and has been the subject of several recent review articles (1, 4-6).

Biology of skeletal growth

Ossification is the process where new bone is made, and occurs by osteoblasts synthesizing bone matrix that subsequently undergo mineralization. The creation of skeletal structures is a complex process, which would normally lead to the child having bones of correct length and proportions with symmetry between the two sides of the body at skeletal maturity.

Skeletal bone is created by two different processes in the growing child. Intramembranous ossification is the creation of bony structures that are not derived from cartilage. This process starts in the mesenchyme covering the brain, and is primarily involved in the development of flat bony structures such as the skull, mandible and partly the clavicle which is considered a mixed intramembraneous and endochondral ossification process. Long bone growth, on the contrary, primarily takes place through creation of cartilaginous tissue that is turned into bone through a process called endochondral ossification. This starts with the creation of primary ossification centres. Mesenchyme differentiates to embryonic hyaline cartilage models surrounded by perichondrium and forms the basis for development of the long bones in the body. In humans bone formation in the femur starts in the 7th foetal week with creation of the diaphyseal centre of ossification. Chondrocytes subsequently undergo hypertrophy, and the cartilage matrix becomes calcified. The surrounding perichondrium develops into periosteum. A thin layer of bone is created as a periosteal bony sleeve that becomes cortical bone reinforcing the bony structures. Vascular tissue invades the diaphysis from the periosteum and progenitor cells enter the created lacunae. These progenitor cells develop into osteoblasts and forms the primitive bone marrow. The creation of trabecular bone begins. These morphologic changes are all together labelled as a primary centre of ossification.

Diaphyseal ossification stops when the process reaches a specialized cartilage zone; the future physis. A secondary centre of ossification will be created in the epiphysis. This will later be covered with joint cartilage in the upward direction and with the physis below. The diaphysis constitutes the central portion of long bones. The physis or the growth plate is located at both ends of long bones and is interposed between the epiphysis and the metaphysis. No significant blood vessels pass through the physis, and chondrocytes are embedded in extra-cellular matrix (7). This highly specialised cartilage tissue can be divided into three different cellular layers with distinct characteristics (8). The zone of reserve is situated below the epiphysis and consists of resting cells that can be moved to the zone of proliferation (9). Cells are arranged in columns and multiply in the zone of proliferation. Matrix synthesis is started which is needed for the process that ensures longitudinal bone growth (10). In the zone of hypertrophy cells enlarge but no more proliferation takes place. The cells continue to be orientated in columns and contribute to the bony elongation process. The most mature layers begin the mineralization process and cells undergo apoptosis. Metaphyseal blood vessels invade the area. New calcified septae are formed where osteoblasts can start synthesising bone matrix and create trabecular bone. Because matrix synthesis, cell division and enlargement takes place in the zone of proliferation and zone of hypertrophy, growth is directed away from the zone of reserve towards the metaphysis. A separate vascular invasion occurs in each end of the long bone and lead to the formation of secondary centres of ossification in the epiphyses. The physis contribute not only to longitudinal bone growth but also diametrical growth of the bone. Specialized cartilage tissue surrounding the physis called the zone of Ranvier is the mechanism behind this. Transverse growth also takes place in the periosteum by a process similar to intramembranous ossification.

The process of regulating skeletal growth consists of genetic, hormonal, nutritional and environmental factors and remains only partially understood (11). Physical activity does appear to be of lesser significance on the final size of the individual. Mechanical factors within normal range seem to have limited effect relative to genetic, nutritional and hormonal controls. Variations in the degree of cell hypertrophy probably contribute to a large portion of differences in growth rate. This process is apparently regulated hormonally (12). The periosteal sleeve is inelastic and tends to resist growth. Could the periosteal sleeve be involved in determining growth rate? Circumcision of the metaphyseal sleeve can be used to stimulate longitudinal bone growth although the outcome is unpredictable (13). It is a well described phenomenon that a fracture with impaired periosteal healing can lead to overgrowth of the affected side (14).

Angulating deformities and leg length discrepancy in growing children

Valgus and varus are terms that define the direction the distal segment of a joint point. Genu valgum is a deformity around the knee joint that refers to outward angulation of tibia in the frontal plane. Conversely, genu varum is a deformity that results in an inward deviation of tibia. In the standing child genu valgum has a knock-kneed appearance whereas children with genu varum appear bowlegged.

In children some degree of knock knee is normal from 3-3.5 years of age (15-19). At that point most children will have 2-3 cm of knock knee defined as the measured distance between the medial malleoli with knees extended. This physiological knock knee will disappear spontaneously when the child reaches 7 year. Obese children are likely to have a larger degree of knock knee than normal weight children (20, 21). In larger degrees of deformities a radiological investigation may be indicated to rule out abnormalities in the physes. Unilateral deformities are often the result of trauma, infection or neoplasms. In late childhood some children can present with bilateral knock knees that is not considered physiological. This condition is called idiopathic genu valgum (IGV) and requires observation as some cases might need specialist orthopaedic care. It needs to be considered if the condition is truly idiopathic or can be attributed to generalized bone diseases as skeletal dysplasia or mucopolysaccharidosis (22). Also genu valgum can be the presenting symptom of rickets (23).

In infancy a mild degree of bow leg can be considered normal. If a larger deformity continues to exist rickets should be excluded. It is uncommon to observe genu varum in childhood or adolescence. A radiological investigation should always be performed. Unilateral deformities presenting with a sharp curvature in the proximal tibia should always raise suspicion of pathology in the proximal tibial physis such as Blount's disease (23, 24).

Leg length discrepancies (LLD) are common conditions with a prevalence of 40-70% in the general population having LLD up to 2 cm (25-28). However, larger discrepancies are reported at much lower prevalence affecting one in every 1000 people (28). It is still unclear what the consequences and outcome of having LLD are. Concerning larger discrepancies investigations has shown that affected individuals can have gait problems and pain arising from the lower back and the knees (29-32). The literature is more conflicting when it comes to the effect of LLD as small as 1 cm with one study reporting increased postural sway (33). On the contrary, another study reports no effect on sway by even larger LLD (34). It is known from a study on reconstruction of posttraumatic bone defects in children that LLD have a serious effect on health-related quality of life using the SF-36 questionnaire (35). Another investigation used the Child Health Questionnaire (CHQ) to assess quality of life in children having LLD. Children with LLD had overall lower values in the psychosocial domain when compared to their healthy peers, but no distinction could be made between children having LLD of less than 2 cm or more than 2 cm (36).

Manipulation of skeletal growth

Bone remodelling continuously takes place in both children and adults. Our present understanding is still based on the concept described in Julian Wolff's monograph on bone transformation from 1892 (37). The observation that bones change its external shape and internal trabecular architecture in response to the forces acting on it is commonly referred to as Wolff's law. This is a concept for modelling and remodelling of bones to adapt to their mechanical environment. Longitudinal bone growth in the immature bone is furthermore influenced by mechanical load and this is believed to be controlled by a concept labelled the Hueter-Volkmann law. Mechanical manipulation of growth was first reported by Carl Hueter in 1862 who

reported on the treatment of children with clubfeet. Through manipulation of the bones the shape could be changed during growth (38). Volkmann describes that changes in compressive forces on a physis would leads to different growth patterns (39, 40). The concept therefore states that compressive forces acting on the physis leads to a reduction in growth velocity and that reduced load increases growth rate. These observations by Hueter and Volkmann have contributed heavily to the development of techniques to manipulate physeal growth in modern paediatric orthopaedic treatment. Frost has later on proposed a concept describing that chondral modelling has one response in relation to physiological loading of the growth plate (41). Both higher or lower physiological load leads to stimulation of growth at the physis (Figure 1).

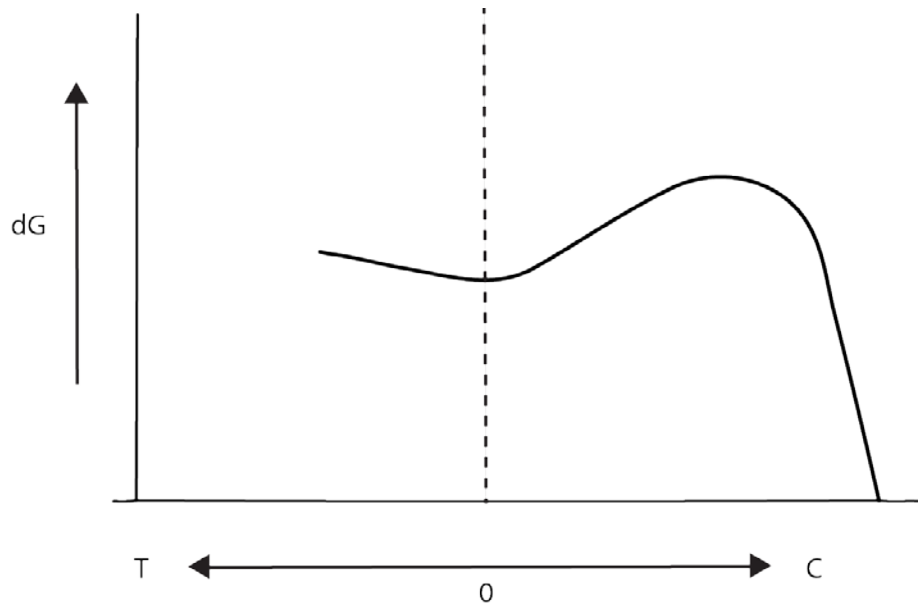

Figure 1: On the x-axis is tension (T) and compression (C) acting on the growth plate. On the ordinary axis is growth velocity plotted as dG. The figure is adapted from Frost (41).

If load of the physis is outside the physiological range a different response is being elucidated with inhibition of growth at the physis. Sustained stress on the growth plate apparently affects growth rate in a linear fashion. These findings takes into account both tensile and compressive forces with tensile forces increasing growth rate and compression decreasing activity in the growth plate (42). The effect on the growth plate by dynamic load is being debated as growth rate has been reported to either being decreased or unaffected (43-45). In gymnasts abnormal ulnar-radial length differences has been reported, which is believed to be caused by great stresses placed on the forearms during gymnastics training (46, 47).

Methods and techniques for guiding growth in bones

Several commonly used treatments in modern paediatric orthopaedics are in fact guided growth using closed methods. Treatment of clubfoot or congenital talipes equino varus (CTEV) has today moved towards the methods taught by Ponsetti. His

treatment consists primarily of serial manipulation and casting of the affected foot. The treatment is started within one or two weeks after birth and the immature skeletal tissue in the foot reacts with correction of the foot deformity resulting in most children avoiding surgery apart from Achilles tendon tenotomi (48, 49). Using ultrasound and magnetic resonance imaging (MRI) it has been demonstrated that the tarsal bones becomes realigned and changes shape during treatment (50, 51). Another condition where closed treatment has a key role in shaping bony structures is Developmental Dysplasia of the Hip (DDH). If left untreated the acetabulum becomes dysplastic and the femoral head becomes less covered by the acetabulum. This condition can lead to a detrimental outcome with pain and early degenerative joint disease. Apparently the growth in depth and width of the acetabulum is dependent on the presence of the femoral head in the joint socket (52). By using a harness or a brace to keep the femoral head located in the acetabulum the hip joint develops normally outgrowing the deformity (53, 54).

Performing a surgical physeal arrest using permanent or potentially reversible techniques may avoid the need for osteotomies in treatment of deformities in growing children. The overall problem with performing a permanent physeal arrest is the need for timing of the procedure. The technique was first introduced by Phemister in 1933 describing a technique to obtain permanent fusion of the growth plate by performing a rectangular resection of bone containing metaphysis, physis, and epiphysis with the resected area subsequently reinserted with ends reversed (55). By using this procedure both equalising of leg length and correction of frontal plane deformities such as genu valgum could be achieved according to Phemister. This procedure has disadvantages including considerable and prolonged postoperative care. When Canale introduced a minimally invasive technique using power drills to permanently destroy the growth plate it gained popularity (56-59). Especially in Europe transphyseal screws are also being used to obtain partial or complete growth arrest. Even though the physis is not destroyed directly by transphyseal screws, this technique is effectively to be considered a permanent fusion of the growth plate necessitating timing of the procedure (60-65).

One of the first attempts to perform a reversible hemiepiphysiodesis was made by Haas who inserted a wire over the physis in growing dogs leading to growth arrest of the affected physis. Because of the seemingly good results he went on and performed surgeries in growing children with LLD. Even though the wire did inhibit growth he also reported on problems with wire breakage (66). Haas continued to work with the wire technique, but also adapted the use of staples to inhibit the growing physis (67).

In 1949, Blount and Clarke reported on stapling of the epiphyseal plate as a method to correct both angular deformities and LLD (68). The paper states that implants should not be left in place for more than 2 years because of the risk for premature closure of the physis. They based this statement on a personal, non-published communication with Phemister. By performing partial epiphysiodesis gradual correction of the angulating deformity was achieved. Bowen described this theory using a graphic representation in 1985 (Figure 2) (69).

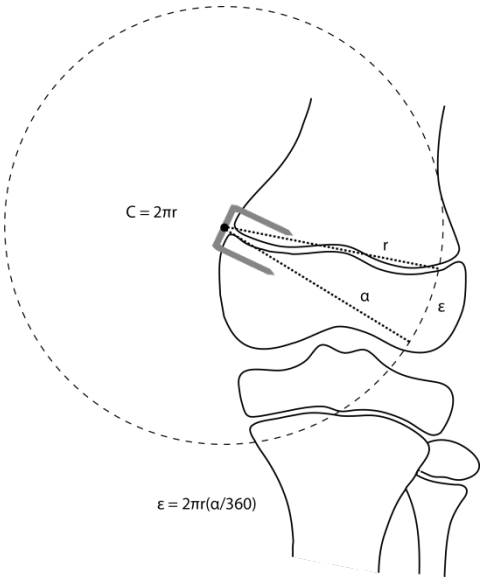

Figure 2: Theory behind hemiepiphysiodesis using staples. The figure is adapted from Bowen (69)

Stapling is now an established procedure that has been used over the last 6 decades. Several papers have addressed the outcome regarding correction of deformities, rebound growth, and hardware failure (70-77). Satisfying results with correction of the deformity is reported in 80- 85% of the cases. Implant failure with staple extrusion or breakage is observed around 10% of the treated physes. Rebound growth is believed to be more likely in children with remaining growth and slightly overcorrection is recommended in children that have not reached skeletal maturity when the deformity is corrected (73). Because of fear of premature closure of the growth plate it has been believed that staple correction for angular deformities should be reserved for older children close to skeletal maturity (20). A more recent study has however demonstrated that stapling can also be performed safely in younger children (78). The actual biological response in the growth plate treated with hemiepiphysiodesis is only partially understood. Staples produce compression over the growth plate which in theory may alter the growth plate permanently. One clinical study demonstrated loss of columnar arrangement of chondrocytes in biopsies from stapled physes from children one year after surgery (79). The effects have been studied in more detail in animal studies. Karbowski et al used skeletally immature pigs that had the medial proximal tibia stapled (80, 81). Histologically they found that the normal columnar pattern of chondrocytes in the growth plate was completely abolished in large areas with severe disturbance of the endochondral ossification. Another experimental study could detect metabolic alterations within a few days after surgery but disturbed mineralization of the growth plate was only seen after prolonged stapling of the growth plate (82). One clinical study has reported that overall leg length will change as a result of hemiepiphysiodesis all though it is unclear if this has clinical relevance (83).

Tension band plating

This is a new technique developed to address some of the complications associated with the use of staples. It was first described by Stevens who developed the eight-Plate implants (Orthofix, McKinney, Texas). These implants have been advocated to

avoid compression of the growth plate and to reduce mechanical failures (2). The tension band plating system consists of a plate which is fixed by one screw on each side of the growth plate. The screws are not rigidly fixed in the plate and can angulate progressively as the deformity is corrected. By using tension band plating implants for hemiepiphysiodesis the fulcrum for growth is in theory moved extra physeal (Figure 3) as compared to stapling where the fulcrum is located at the crossbar of the staple (Figure 2).

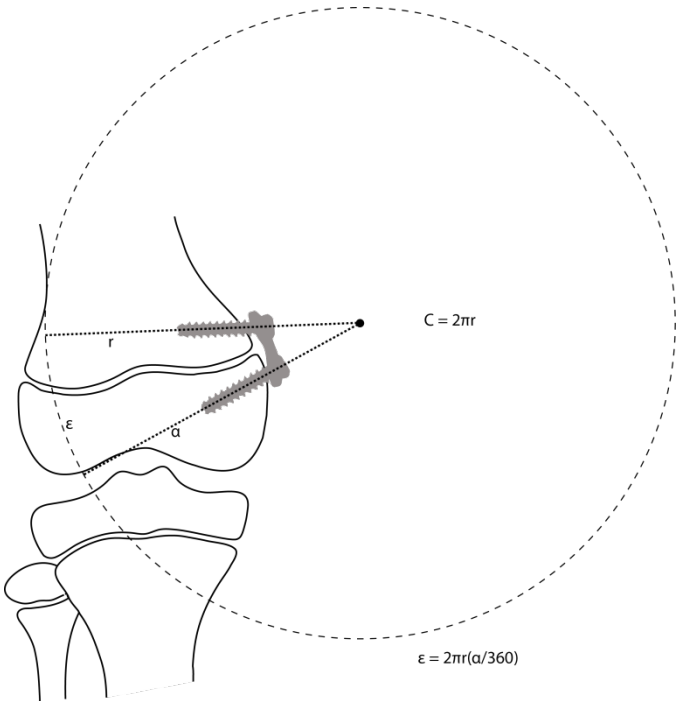

Figure 3: Theory behind hemiepiphysiodesis using tension band plating.

This displacement of fulcrum for growth around the physis would in theory lead to a different load of the physis resulting in a faster correction of the deformity (2, 69). The tension band plating technique appears to be safe and an approximately 30% faster correction rate was reported in the first paper on its use (2). Since then a number of publications has focused on the use of tension band plating with all studies being retrospective but one (84-89). Overall results seem satisfying and the tension band plating technique has now partly replaced stapling. The only prospective study published so far comparing staples and tension band plating (non-randomised) were unable to detect any difference between the treatments (86). Complications to the tension band plating technique reported so far have been very few. Two publications focus on hardware failure of the Orthofix implants (90, 91). Children suffering from pathological physis such as Blount's disease are much more likely to experience hardware failure or extrusion of implants during treatment (92). These complications have since led the companies to develop solid screws that can be used in patients with high risk for hardware failure. Another indication for use of tension band plating appear to be anterior placement of implants to correct fixed knee flexion deformity (FKFD) with one paper reporting good results (93). A stress fracture around the knee after this application of tension band plating for FKFD has been reported (94). The use of anterior placed tension band plating on distal tibia to

treat equino deformity has been investigated and even though some radiological correction does happen it does not change the overall problem (95). Furthermore this technique might lead to creation of a physeal bridge (96).

Two types of tension band plating implants were compared in an experimental setup favouring the Peanut plate (Biomet, Warsaw, Indiana) system towards the eight-Plate because of less ability to breakage (97). Solid screws were overall stronger than canulated screws with the strongest construct being stainless steel Peanut plate with solid screws. Authors recommend the use of solid screws for treatment of obese children with Blount's disease. A number of experimental animal studies have been published on the use of the tension band plating technique (98-102). In one animal study rabbit hind limbs were allocated to either lateral stapling, lateral tension band plating, sham surgery or no surgery (98). Staple migration was observed after 2 weeks treatment. No results from the histological analysis were reported apart from the growth plate appearing disturbed between the staple legs. Interestingly staple hemiepiphysiodesis produced a larger valgus deformity when compared to the tension band plating technique. A quite similar result was observed in another study on rabbits but better grasp in bone was reported for the implants used for tension band plating (100). In their histological analysis cellular disorganisation was reported around implants in 9 preparations from a total of 34 femurs. No differences were found between implant types and implant related injuries to the growth plate were not observed. Two porcine animal studies compared stapling with tension band plating in paired setups similar to the study presented (99, 101). Medial hemiepiphysiodesis induced a varus deformity using both techniques but the angulation created was larger using tension band plating technique. Signs of early loosening of staples as well as failure of implanted staples were reported. No histological analysis was included in these studies. A recent study investigated the effect of screw length on rate of creation of deformity but found no difference between short and long screws. However guided growth using the tension band plating technique was overall found to be more efficient than staples (102).

Aim of the thesis

a) To compare the primary effect of stapling and tension band plating on the physis in an animal model (Paper I)

b) To compare the effect of stapling and tension band plating on the physis after resumption of growth in an animal model (Paper I)

c) To prove temporary epiphysiodesis using tension band plating as a potential treatment for leg length discrepancy (Paper II)

d) To compare the clinical and radiological effects of stapling with those of tension band plating in a group of children with idiopathic genu valgum (Paper III)

Materials and methods

Hypotheses

I) Tension band plating induces less change in growth plate morphology compared to staples

II) Tension band plating can induce temporary growth control

III) Tension band plating provides a faster correction rate compared to stapling

Study designs

The studies used for (I) and (II) was conducted using a large animal model. A paired setup was used to reduce variance between individuals, to minimise the number of animals needed, and to compensate for loading differences between sites of epiphysiodesis. The studies were performed at two different institutions with Study I being carried out at the Department of Animal Health and Bioscience, Foulum, Aarhus University. Study II was performed at Clinical Institute, Aarhus University Hospital (AUH) because of the close relationship with the MR-research centre. Study III was conducted at Department of Children's Orthopaedics at AUH and Department of Orthopaedics at Hospital Unit West.

Study I: Implants were applied over proximal medial tibia spanning the growth plate. Right medial proximal tibia was randomized to either unilateral stapling or tension band plating. The left side received the opposite treatment (Figure 4).

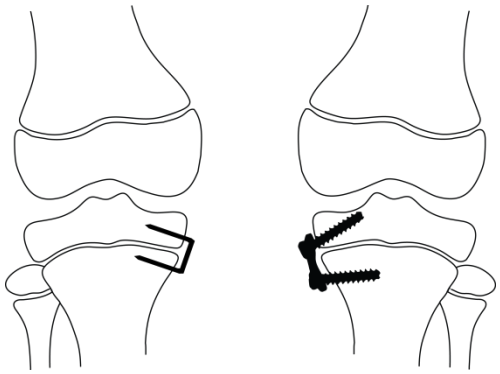

Figure 4: Medial proximal tibia randomized to either stapling or tension band plating hemiepiphysiodesis.

Two groups of animals were studied. In the first group (A) the primary effect of epiphysiodesis on the growth plate was studied. Animals received surgery and were followed for 9 weeks. In the second group (B) the delayed growth plate response to partial epiphysiodesis was studied. In this group of animals implants were removed after 9 weeks of housing and the animals were followed for an additional 5 weeks (Figure 5).

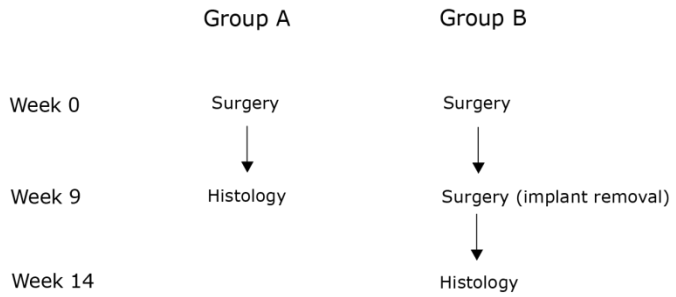

Figure 5: Flowchart of the animal experiment in Paper I.

Study II: The setup was designed to validate the ability of the tension band plating technique to induce a temporary growth arrest in a long bone. The paired setup described in Study I was used again but differed in several ways. One group of animals was used. The right proximal tibia was randomly allocated to temporary epiphysiodesis using medial and lateral tension band plating or no treatment (Figure 6).

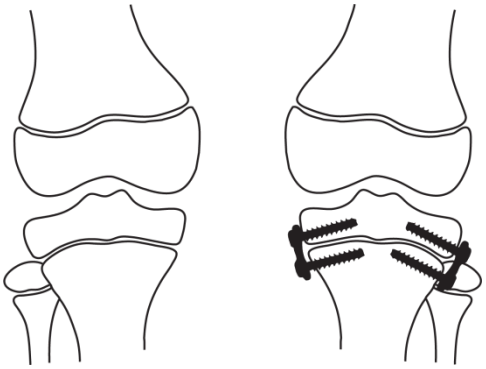

Figure 6: Proximal tibia randomized to either medial and lateral tension band plating or no treatment.

The left proximal tibia received the opposite treatment of the right side. The implants were removed after 10 weeks. The resumption of growth was then studied for 5 additional weeks (Figure 7).

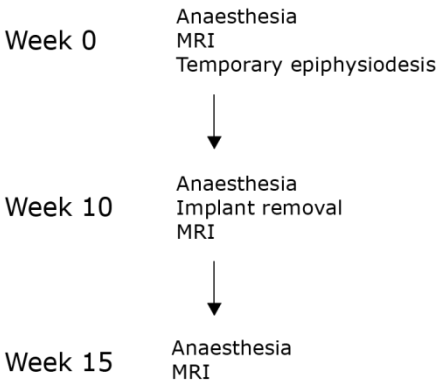

Figure 7: Flowchart of the animal experiment in Paper II.

Study III: The final paper was based on a randomized clinical trial (RCT) on treatment of IGV. Children included in the study were randomized to either medial tension band plating (Figure 8) or stapling (Figure 9) of the distal femoral growth plates

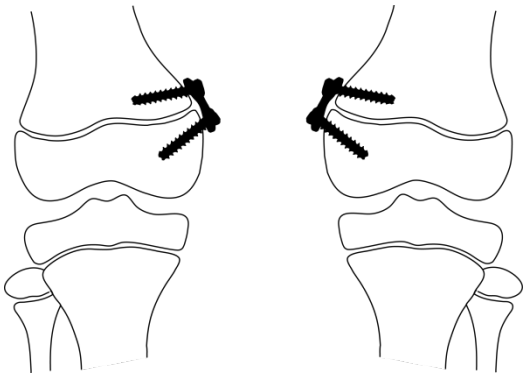

Figure 8: Medial tension band plating hemiepiphysiodesis applied to the distal femoral physes.

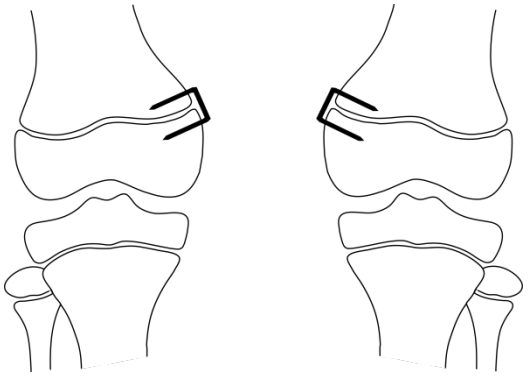

Figure 9: Medial stapling hemiepiphysiodesis applied to the distal femoral physes.

After randomization, the two groups of children were followed in the same way with regular examinations in the outpatient clinic. Minimum time between visits in the clinic was 3 months. The advantage by doing a randomization is that it minimizes allocation bias and balances both known and unknown prognostic factors. 26 envelopes were made for randomisation; 13 for stapling, and 13 for tension band plating. The envelopes were mixed and numbered in random order. Finally the envelopes were placed in chronological order and divided between the two hospitals. All operating surgeons were familiar with both stapling and tension band plating.

Animal model

A large number of studies concerning mechanical retardation of bone growth have been conducted in several different species. Commonly used animals are; rats (42, 103), rabbits (98, 100, 102, 104), sheep (105, 106), pigs (80-82, 99, 101) and dogs (66, 107). The pig was chosen for Paper I and II for a number of reasons. Several studies have already used the same model to study hemiepiphysiodesis (80-82, 99, 101). It was planned to use commercially available implants in clinical use for similar procedures and this required us to use an animal of a certain size (108). Pigs

weighing more than 30 kilos have appropriately sized proximal tibias suitable for the planned procedures and the proximal tibia can easily be accessed using small incisions (Figure 10) (109).

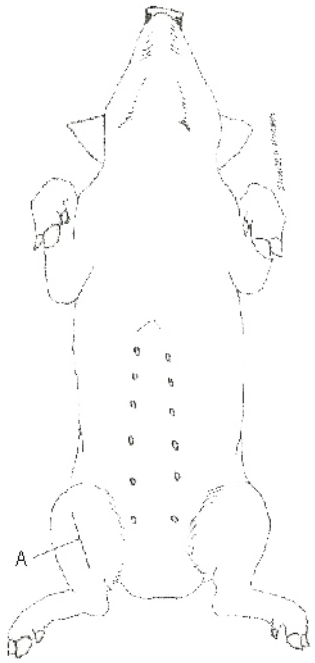

Figure 10: Pig in supine position with access to medial proximal tibia (A). The figure is from M. Michael Swindle; Swine in the laboratory (109).

The animals used were 10 weeks old skeletally immature Danish domestic pigs. The appearance of the pig growth plate at the proximal tibia is quite similar to that of humans. Furthermore is porcine bone considered to be a suitable model for comparison with human bony tissue (110, 111). Porcine bone also shares characteristics with human bone concerning mineral composition, regeneration and cortical mineralization (112-115). Another important reason to use the pig is the long history of research in this animal at Aarhus University. Pigs have been used in studies on scoliosis, cartilage tissue and implantable scaffolds. One of the two institutions used for conducting the studies has strict regulation against contact with animals that can transfer Creutzfeldt–Jakob disease. Sheep and goat could therefore not be used for the experiments even though they potentially have certain advantages compared to pigs as longitudinal bone growth is considered to be faster.

Patients in the clinical study

Children age 8 – 15 years with a severe condition that were limiting in daily activities were considered eligible for inclusion in the trial if they had an intermalleolar distance of at least 7 cm. At least 6 months of estimated remaining growth was needed. Children with unilateral conditions or pathological growth plate disease such as Ricketts were excluded. This was done to avoid bias from children that had abnormal growth in the treated physis. For instance in Blounts disease the degree of deformity before initiation of the corrective procedure seems to correlate with outcome (116).

Ethics

The experimental protocol for (I) and (II) was in accordance with the Danish Animal Research guidelines and the experiments was approved by the Danish Animal Experiment Committee (study J.nr 2008/561–329).

The clinical study (III) was approved by the Central Denmark Region Committees on Biomedical Research Ethics (J.nr M-20080147). The study was registered with the Danish Data Protection Agency (J.nr. 2009-41-3248). Informed and written consent were obtained from all parents to children included.

Histomorphometry (I)

Growth plate morphology was studied by performing histomorphometry on sampled growth plate tissue. The growth plate is a complex structure with regard to morphology and the proximal tibia is an asymmetric structure. The anisotropic orientation of the tissue necessitates several rules to be respected when sampling tissue (117). Samples of the epiphyseal growth plate and metaphysis were taken in a standardized manner from the medial aspect of the knee joint. The long axis of the tibia was defined as the line connecting the anterior cruciate ligament (ACL) with the middle of the ankle joint line. The ACL and medial border of the tibia was defined. The middle of this line was located in the centre of the medial tibial plateau and was defined as the region of interest (ROI). With reference to this point samples were taken in the long axis of the tibia. A hollow drill (14 mm) was used to cut a 30 mm long cylinder exactly parallel to the long axis of the tibia consisting of cartilage, epiphysis, physis and metaphysis. The sampled tissue was dehydrated in graded ethanol (70-100 percent), and embedded in cold methyl methacrylate (MMA). The samples were cut in 7 μm thick frontal sections on a microtome (Biomaterial Research Group, Leiden University, The Netherlands) from the outer rim of each biopsy. 2 sections were kept for each 500 μm ending up with 8 sections from 4 levels (118). These sections were stained with haematoxylin and eosin (HE).

Several papers report on quantification of growth plate chondrocyte layers. In a paper from 2002 Stokes et al investigated the effect of compression on rat tail vertebra (103). Fractions of the chondrocyte layers (zone of reserve, zone of proliferation and zone of hypertrophy) were determined using quantitative histomorphometry. The cellular layers were defined according to previous studies on growth plate histomorphometry by Nutall and Byers (Figure 11) (8, 119).

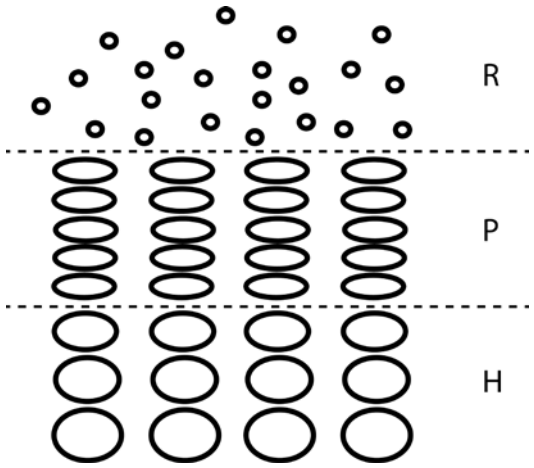

Figure 11: Schematic drawing of the growth plate chondrocyte layers; R, zone of reserve; P, zone of proliferation; H, zone of hypertrophy. Adapted from Nuttall (8).

The cartilaginous zone of reserve was defined as the region from the secondary centre of ossification to the region where chondrocytes become aligned in columns. The zone of proliferation was comprised of columnar chondrocytes of constant size. Finally the zone of hypertrophy consisted of all enlarged chondrocytes distal to the proliferative zone and proximal to the primary centre of ossification. Areas in the growth plate with disorganized cartilage tissue (normal columnar appearance of the cell distribution were lost) were also determined. The analysis was performed using a standardized setup on slice 2 and 4 (1000 µm distance between sections). An Olympus BX 50 microscope modified for stereology was used. A video camera was attached to the microscope. The microscopic field was transmitted to a computer monitor and a stereological software programme was applied (newCAST, Visiopharm, Hoersholm, Denmark) for histomorphometry. Fractions of chondrocyte layers were determined by point counting (120). As a rule-of-thumb sampling intensity of any given tissue should be of a minimum of 50 hits per sample (121). The ROI was defined as all visible physeal cartilage on each section. At 10x magnification rate 100% of this area was sampled using 3 x 3 = 9 points on the screen. Based on a pilot analysis this setup ensured a sufficient sampling intensity. The height of the growth plate was established as an average value from each sample. Using repeated height measurements from each section (perpendicular to the growth plate at 5 different intersections with a distance of 1mm between the measurements) mean values were determined. Sections from 5 random animals were analysed twice and used for reproducibility measurements.

Magnetic Resonance Imaging (II)

Plain radiographs are still considered the gold standard for imaging of bone, but when it comes to imaging of the cartilage physis in the growing bone x-ray is an indirect measure because cartilage tissue is radio lucid (122). This has led to widespread experimental and clinical research in the use of MRI of the growth plate and surrounding tissues (123-125). In daily orthopaedic paediatric practice MRI is now a routine investigation in assessment of integrity of the growth plate after for instance skeletal injury. MRI of the growth plate may also be useful in monitoring of skeletal toxicity during drug treatment (126, 127). MRI has been used to follow

children undergoing normal physiological physeal closure as well as to evaluate the effect of epiphysiodesis in both clinical and experimental studies (128-130). It is possible to avoid using intravenous contrast (Gadolinium), and still get useful information from the epiphysis and metaphysis. This is particularly useful when edema is involved (131). Administration of contrast is unacceptable in relation to the paediatric population. Apart from toxicity it can cause confusion and in fact complicate the interpretation of the images (132). Recent papers has looked into the subject of detection changes in solid biomaterials such as bone using short (or even ultra-short) echo times MRI (133-135). This has proven useful as a noninvasive method to study biochemical or metabolic changes in tissue. In bone marrow water content and lipid signals is of particular interest.

A Siemens Magnetom Avento 1.5 Tesla clinical scanner was used to run 4 multiple-slice (25 coronal images) sequences on both tibiae. One 11 cm diameter surface coil was applied to the proximal tibia. To avoid artefacts from the implants the scans were performed at baseline before surgery (0 weeks), immediately after implant removal (10 weeks), and before euthanasia (15 weeks). All scans were performed with the animal under general anaesthesia.

The following sequences were obtained:

1) High resolution T1-weighed (echo time 20 milliseconds, repetition time 800 milliseconds, slice thickness 3 mm, echo train length 1, number of averages 2, FoV 120 x 120 mm and resolution 384 x 384 pixels)

2) Water content estimation T1-weighed (echo time 1.61milliseconds, repetition time 15 milliseconds, slice thickness 4 mm, echo train length 1, number of averages 3, FoV 101 x 180 mm and resolution 512 x 288 pixels)

3) T2-weighed (echo time 41 milliseconds, repetition time 2000 milliseconds, slice thickness 3 mm, echo train length 7, number of averages 2, FoV 140 x 140 mm and resolution 896 x 896 pixels)

4) T1-weighed sequence of the whole tibia (echo time 20 milliseconds, repetition time 800 milliseconds, slice thickness 3 mm, echo train length 1, number of averages 2, FoV 89 x 220 mm and resolution 384 x 156 pixels).

Image processing was performed with all information on Dicom images being removed before processing. However because traces after implants can be seen on the images complete blinding could not be assured. Siemens software (syngo-Fastview, Siemens AG, Berlin and München 2004 - 2008) was used to perform measurements of the distance between the proximal and distal physes (sequence 4). In slice 14 and 15 of each tibia the distance was measured at 3 fixed positions (medial, central and lateral) (Figure 12).

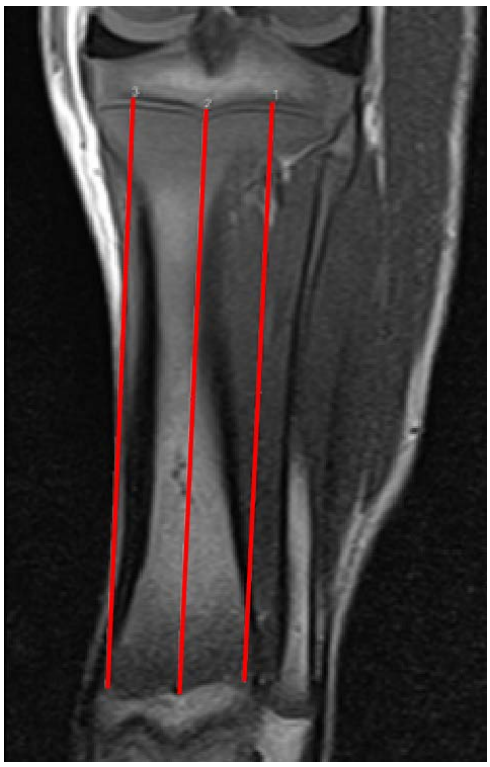

Figure 12: Measurement of the distance between the distal and proximal physis on whole tibia T1 MR images.

Spatial identical ROIs were applied to slice 14 and 15 on short echo time T1-weighted images (sequence 2) and mean pixel values calculated (SisWin, Steffen Ringgaard, MR-research centre, Aarhus University Hospital). Changes in signal intensity on these images correspond to changes in water content in the bone marrow. Using this software, measurements were performed standardized and this circumvented the need for plotting freehand ROIs (Figure 13).

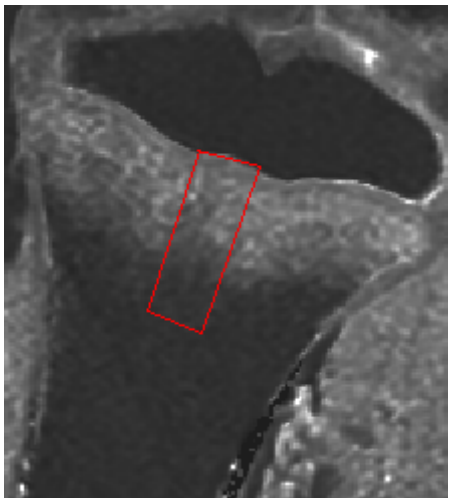

Figure 13: Quantification of metaphyseal water content on short echo time T1 MR images using SisWin.

Average values between the slides were used for statistical analysis. The status of cartilage tissue in the proximal tibia was assessed on series of images from all 3 scanning sessions (sequence 1 and 3).

Radiographic imaging (III)

Literature on the reliability of performing long standing radiographs in children is sparse. Most publications focus on adult patients with degerative conditions in the knee joint. It is important to secure correct rotation of the lower limb by using anatomic landmarks such as the posterior part of the femoral condyles (136). At the beginning of the radiographic procedure an exact lateral image was obtained using fluoroscopy with the posterior part of each femoral condyle being used as reference. A footprint was drawn at the floor to be able to reproduce the position of limb for the final radiograph. All knee joints were fully extended because differences in the mechanical axis between full extension and 20 degrees of flexion are negligible (137). This work by Sanfridsson et al recommends actually the use of a semi flexed position to avoid fixating the knee joint. On the contrary it was chosen at AUH to lock the knee in a fully extended position to minimize the risk of unwanted rotation of the knee. One standing anterior-posterior recording was taken with both lower extremities exposed at the same time. To minimize parallel axis error a distance of 3.5 m was chosen which is in accordance with other published works and Paley's book on deformity correction (136, 138-142). The beam was centred on level with the knees. Images were saved in the picture archiving and communication system (PACS).

Studies on guided growth of the lower limb usually report radiographic findings but different measurements are being used. Some studies use the angle between the femoral mechanical axis and the tibial mechanical axis (77, 89). The most generally accepted measurements are the parameters described by Paley (139). Mechanical axis deviation (MAD) was measured by marking a point at the centre of the femoral head and at the centre of the ankle joint. These points are then connected forming the lower extremity mechanical axis. A point is then drawn at the centre of the knee joint and the MAD is then measured as the perpendicular distance in millimetres from the centre of the knee joint to the lower extremity mechanical axis. The lateral distal femoral angle (LDFA) is measured between the femoral mechanical axis (made of a line connecting the centre of the femoral head and the centre of the knee joint) and a line drawn along the inferior aspect of the femoral condyles. Finally the medial proximal tibial angle (MPTA) is measured between the tibial mechanical axis (the line connecting the centre of the ankle joint and the centre of the knee joint) and a line drawn along the tibial plateau. It has been shown that these measurements can be reproduced both within and between observers with good reliability (143, 144). Furthermore digital radiographs can be measured reliably and then used for treatment decisions (145).

Clinical parameters (III)

Treatment time from index surgery to removal of implants was calculated and used for the analysis. Clinical examinations of the children were conducted in the outpatient clinic by experienced observers only. Measurements of intermalleolar distance were documented in the charts and performed with the children weight

bearing. In theory laxity of the medial collateral ligament might lead to an increase in the measured intermalleolar distance in weight bearing children compared to supine children. Only weight bearing measurements were performed as this was the standard procedure at both the involved departments and the recommended examination according to several studies (17, 19).

The visual analog scale (VAS) score was used to estimate pain in children every 12 hours for 72 hours after index surgery. A scoring system consisting of a vertical line of 80 mm was used. This scoring system is considered valid to measure pain in children (146, 147). Furthermore, postoperative consumption of analgesics (paracetamol, ibuprofen, codeine and morphine) was registered on the day of surgery and continued for 3 days. The postoperative pain care regime is outlined in Table I.

Table 1: Pain care regime.

	Weight < 40 kg	**Weight > 40 kg**
Before surgery:	Paracetamol 10/kg Ibuprofen 10/kg	Paracetamol 1000 mg Ibuprofen 400 mg
Soft tissue infiltration	0.5 ml / kg Bupivacaine 5 mg/ml + Adrenalin 5myg/ml	0.5 ml / kg Bupivacaine 5 mg/ml + Adrenalin 5myg/ml
Postoperative	Paracetamol 10/kg x 4 Ibuprofen 10/kg x 3 Supple. Morphine 0.2-0.4mg/kg	Paracetamol 1000 mg x 4 Ibuprofen 400 mg x 3 Supple. Morphine 0.2-0.4mg/kg

No patient reported outcome (PRO) scoring system exists for children with specific emphasis on disorders around the knee. The Paediatric Orthopaedic Society of North America (POSNA) paediatric score (which is freely available on the web) is not translated and validated for use in Denmark (148). This is a general problem in relation to assessment of outcome in clinical studies on musculoskeletal disorders in children. The only validated PRO scoring system available at the moment is the Oxford score of foot and ankle questionnaire (OxFAQ) (149). This PRO is in the process of being translated and validated in Denmark. A general PRO score for paediatric outcome also exist; CHQ which has previously been translated to Danish and validated (150).

Statistical considerations

Samples sizes

Normal proportions of the reserve, proliferative, and hypertrophic zones were unknown at initiation of the experiment (I). Based on a paper on histomorphometry of the porcine proximal tibial growth plate normal reserve zone was estimated to constitute 33% of the growth plate cartilage (151). Because tension band plating was considered a more biological growth inhibition the fraction of the reserve zone was

expected to remain at 33% when using tension band plating and to be increased to 41% when using stapling. Estimated standard deviation is 6 % based on results from another porcine experimental study (152). The desired power is 80 % and alfa = 0.05. Based on this it was estimated that a design with 2 x 9 animals would be appropriate. One additional animal was allocated to sham surgery in each group.

A pilot study with similar size animal and implants was conducted prior to the study (II). A LLD was created without hardware failure being noted. This animal was not included in the study. A 15 mm mean increase in interphyseal distance was expected when the control side is compared to the treated side. Estimated standard deviation was 7 mm. The desired power was 90 % and alfa = 0.05. Five animals were included in the study.

Based on data available in literature during planning of the clinical study (III) expected mean treatment time for tension band plating is 9.33 months (2). Expected standard deviation was 3 months based on the same paper. Mean treatment time with staples was expected to be at least 13 months. In fact some older papers recommend 18 months of mean treatment with staples so this would be a rather optimistic estimate. Power was set at 80 % and alfa = 0.05. Based on these assumptions 11 children should be included in each group. A total number of 26 children were chosen to cover for drop outs in the study period.

Reproducibility

Inter-individual differences arising from biological factors typically constitute the largest source of variation in any morphological analysis of biological tissue (153). Error variance from all levels of within-individual sampling is expressed in terms of the coefficient of variation (CV) which can be expressed as:

$$CV = \frac{\sqrt{\frac{1}{(2k)}\sum_1^k d^2}}{\bar{x}}$$

Where,

CV = coefficient of variance

k = number of double estimates

d = difference between first and second estimates

$\bar{x}$ = mean value of first and second estimate

Reproducibility of histomorphometry (I) was estimated by performing double height measurements and determination of growth plate chondrocyte fractions on 5 random specimens (10 histological sections) with at least one month between measurements. CV for height measurements was 3.1%. For determination of growth plate chondrocyte fractions CV values were 7.5 % for zone of reserve, 7.1% for zone of proliferation, 10.5 % for zone of hypertrophy and 7.0% for disorganized cartilage tissue.

Reproducibility of data derived from MRI (II) was estimated by doing double measurements on all slices. The coefficient of variation for interphyseal distance at

baseline/10 weeks/15 weeks was 0.6%/1.8%/0.4% and for mean values on water estimation T1 weighted MRI at baseline/10 weeks/15 weeks was 2.4%/5%/1.9%.

As mentioned above the total variation is mainly determined by the biological variance and the analytical variance in these studies probably only plays a minor role as observed by the CV values that were well below the acceptable range of 20%. CV values of less than 10% are in general considered good reproducibility.

In the clinical study (III) inter- and intraobserver reliability of measurements on long standing x-rays was estimated by calculating Intra Class Correlations (ICC) coefficients. Two different observers performed the measurements independently on the radiographs twice with at least one month between measurements. Interobserver reliability for LDFA, MPTA and MAD was calculated with ICC coefficients ranging from 92-97 % / 83-84% / 99-100% respectively. Concerning intraobserver reliability corresponding ICC coefficients for LDFA, MPTA and MAD was 98 % / 90 % / 100 %. ICC coefficients > 80% can be viewed as good reliability. The primary measurements performed by MBH were used for statistics in Paper III.

Statistics

Normality and equal variance of the data were examined first. Based on probability plots and Shapiro-Wilks tests data was found normally distributed in (I-III) and hence parametric statistics were used. A paired t-test was used to test for differences in growth plate chondrocyte fractions between implants in Study I. Histomorphometric data was compared between group A and B using Students t-tests. A paired t-test was similarly used to compare measurements of interphyseal distance and water content values in Study II. In the clinical Study III groups were compared using Students t-tests. P-values < 0.05 were considered to be significant. Mean values with ranges were used in Paper I-II. In Paper III the 95% confidence intervals were given. Coefficients of variation (I-II) were calculated using Microsoft Excel 2010. ICC coefficients (III) were calculated using a One-way Analysis of Variance. The effect size in Study III was calculated as Cohen's delta defined as the difference between the two means divided by the standard deviation for the data. The Intercooled Stata 11.2 (StataCorp, TX, USA) statistical analysis package was used for statistical computations (I-III).

Summary of Results

Paper I: Similar growth plate morphology in stapling and tension band plating hemiepiphysiodesis. A porcine experimental histomorphometric study

In a porcine experimental study two groups of animals had right proximal tibia randomised to medial epiphysiodesis by either stapling or tension band plating. Left side received the opposite treatment. In group A (n=10) the primary effect of epiphysiodesis on the growth plate was studied. Animals received surgery and were followed for 9 weeks. In group B (n=8) the delayed growth response after partial epiphysiodesis was studied. In this group implants were removed after 9 weeks of housing and the animals were followed for an additional 5 weeks. Fractions of the chondrocyte layers were determined using quantitative histomorphometry. Areas in the growth plate with disorganized cartilage tissue were also determined. Histological images can be seen in Figure 14.

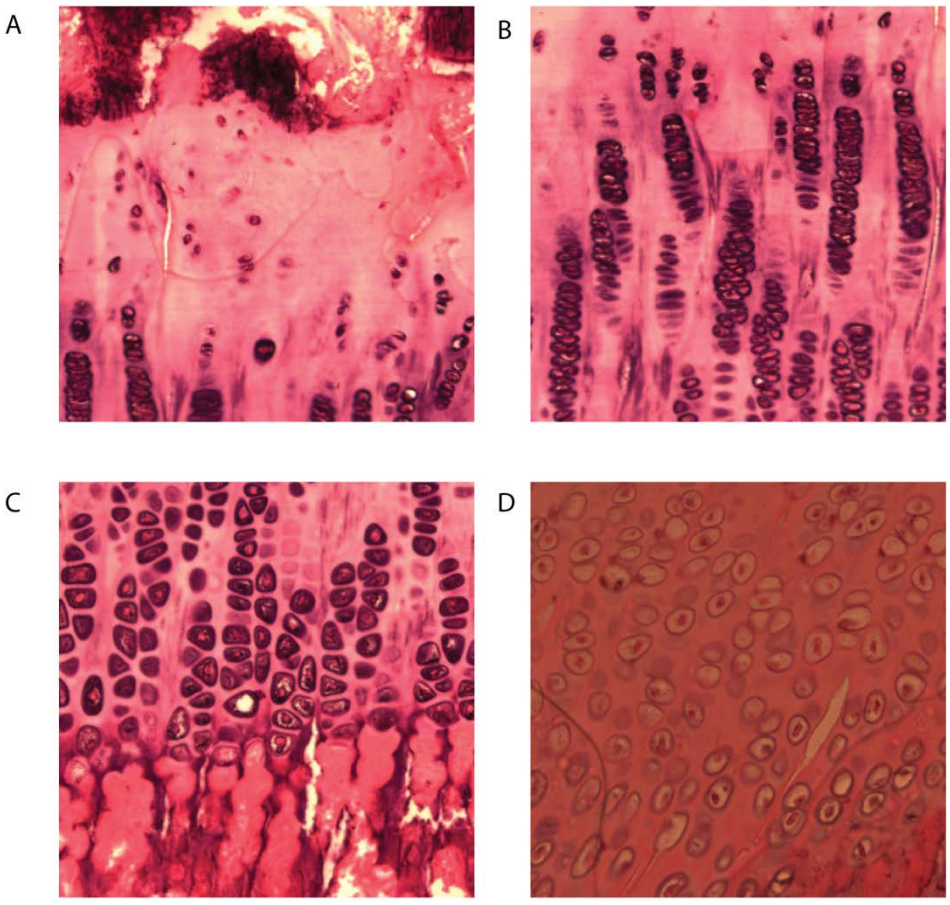

Figure 14: Histological images showing; A, zone of reserve; B, zone of proliferation; C, zone of hypertrophy; D, disorganized cartilage tissue. HE staining. 460 times magnification.

The height of the growth plate was established as an average value from each sample. Data were analysed using Paired t-tests. No statistical significant differences between stapling and tension band plating were found in distribution of growth plate chondrocyte layers, disorganized cartilage, or height of the growth plate in the primary effect group (A) (Table 2). In the delayed response group (B) no significant differences were observed in chondrocyte zone fractions, disorganised cartilage tissue, or average heights of the treated growth plates when comparing stapling and tension band plating (Table 3). The fraction of disorganized cartilage now represents more than one third for both staples and tension band plating. In group B a significantly increased height of the growth plate was observed compared to group A (Table 4). Disorganised cartilage tissue in the growth plate was primarily visible in samples from study B. Areas without normal columnar arrangement of chondrocytes were observed in 2/20 samples from study A and in 13/16 samples from study B. Disorganized cartilage tissue were observed after both treatment with tension band plating and staples. Data on the two animals receiving sham surgery can be seen in Appendix 1.

Table 2. Study on the primary effect of hemiepiphysiodesis for 9 weeks (group A). Mean values (ranges) of fractions of the different layers of the growth plate are given.

	Tension band plating (n=10)	Stapling (n=10)	P-value
			0.55
Zone of reserve	0.39 (0.29 – 0.62)	0.40 (0.28 – 0.51)	0.65
Zone of proliferation	0.39 (0.29 – 0.44)	0.40 (0.31 – 0.51)	0.60
Zone of hypertrophy	0.20 (0.09 – 0.28)	0.20 (0.15 – 0.29)	0.15
Disorganized cartilage	0.01 (0 – 0.12)	0	0.50
Growth plate height (um)	572 (436 – 814)	546 (450 – 737)	0.55

Table 3. Study on delayed response to hemiepiphysiodesis 5 weeks after removal of implants (group B). Mean values (ranges) of fractions of the different layers of the growth plate are given.

	Tension band plating (n=8)	Stapling (n=8)	P-value
Zone of reserve	0.23 (0.02 – 0.42)	0.30 (0.16 – 0.54)	0.46
Zone of proliferation	0.27 (0.02 – 0.51)	0.21 (0.06 – 0.40)	0.46
Zone of hypertrophy	0.15 (0 – 0.25)	0.14 (0.03 – 0.25)	0.83
Disorganized cartilage	0.35 (0 – 0.96)	0.35 (0 – 0.74)	0.92
Height of growth plate	1979 (1066 – 3536)	2075 (927 – 4234)	0.75

Table 4. Comparison between group A and B. Mean values (ranges) between right and left side from each animal is used. Fractions of the different layers of the growth plate are given.

	Group A (n=10)	Group B (n=8)	P-value
Zone of reserve	0.39 (0.29 – 0.44)	0.26 (0.12 – 0.35)	0.003
Zone of proliferation	0.40 (0.33 – 0.55)	0.24 (0.07 – 0.42)	0.01
Zone of hypertrophy	0.20 (0.12 – 0.27)	0.14 (0.03 – 0.25)	0.11
Disorganized cartilage	0.01 (0 – 0.06)	0.35 (0.01 – 0.72)	0.002
Height of growth plate	559 (473 – 710)	2027 (1123 – 3851)	> 0.001

Paper II: Controlled longitudinal bone growth. An experimental study.

In order to study growth control in long bones a porcine experimental model with 10 weeks old animals was used (n=5). Right proximal tibia was randomized to temporary epiphysiodesis using tension band plating or no treatment. The left side received the opposite treatment. At the beginning of the experiment MRI was performed after induction of anaesthesia and surgery was performed. After 10 weeks of housing the implants were removed in a second surgical procedure and a second MRI was performed. The animals were followed for an additional 5 weeks to study resumption of growth. At the end of the study a final third MRI was done. The distance between the distal and proximal physis was measured on MR images using a standardized setup. Metaphyseal water content in the proximal tibia was quantified by applying regions of interests on the images. Paired t-tests were used to compare values from intervention and control side. A significant difference was found in the distance between the distal and proximal physis after implant removal with the control side being longest (Table 5). At the final MRI this difference in distance between control and intervention side is still observed. After temporary epiphysiodesis water content was significantly lower compared to the control leg (Table 6) (Figure 15). At the end of the experiment water content returns to values within the range of the control leg (Figure 16).

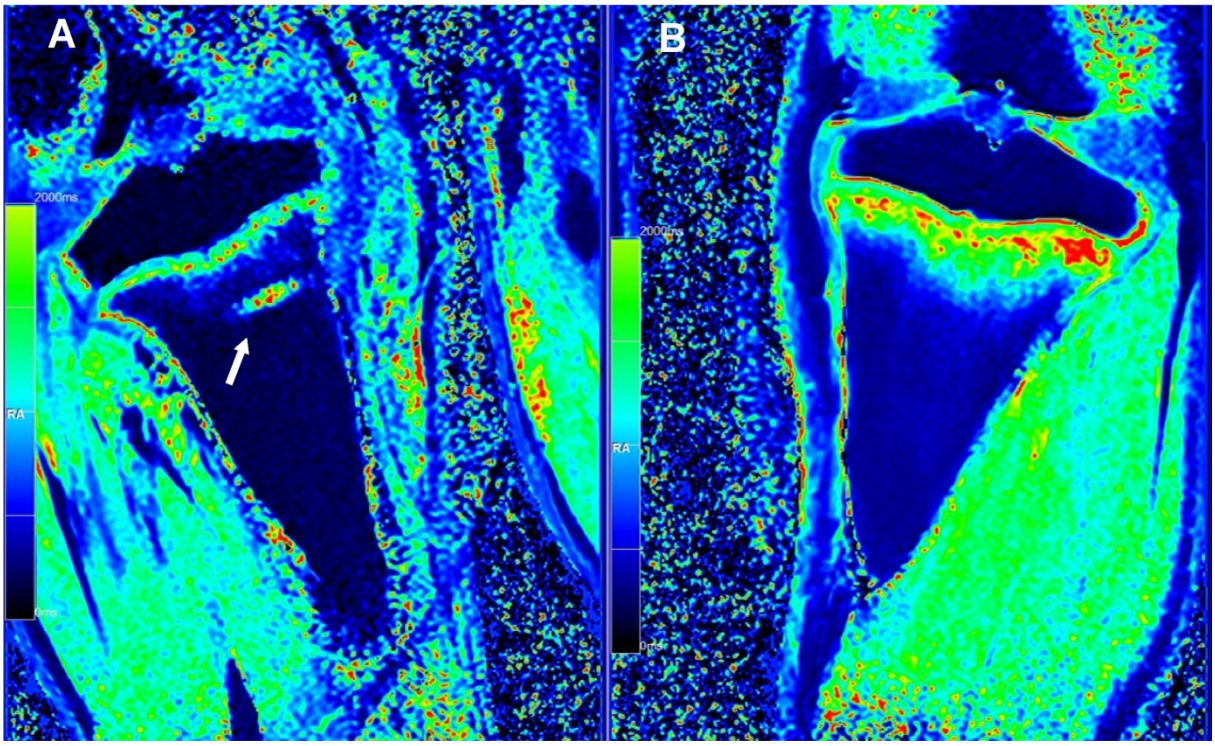

Figure 15: 10 weeks of treatment. T1 MR images (A = tension band plating and B =control) immediately after removal of implants. White arrow marks trace after metaphyseal screw).

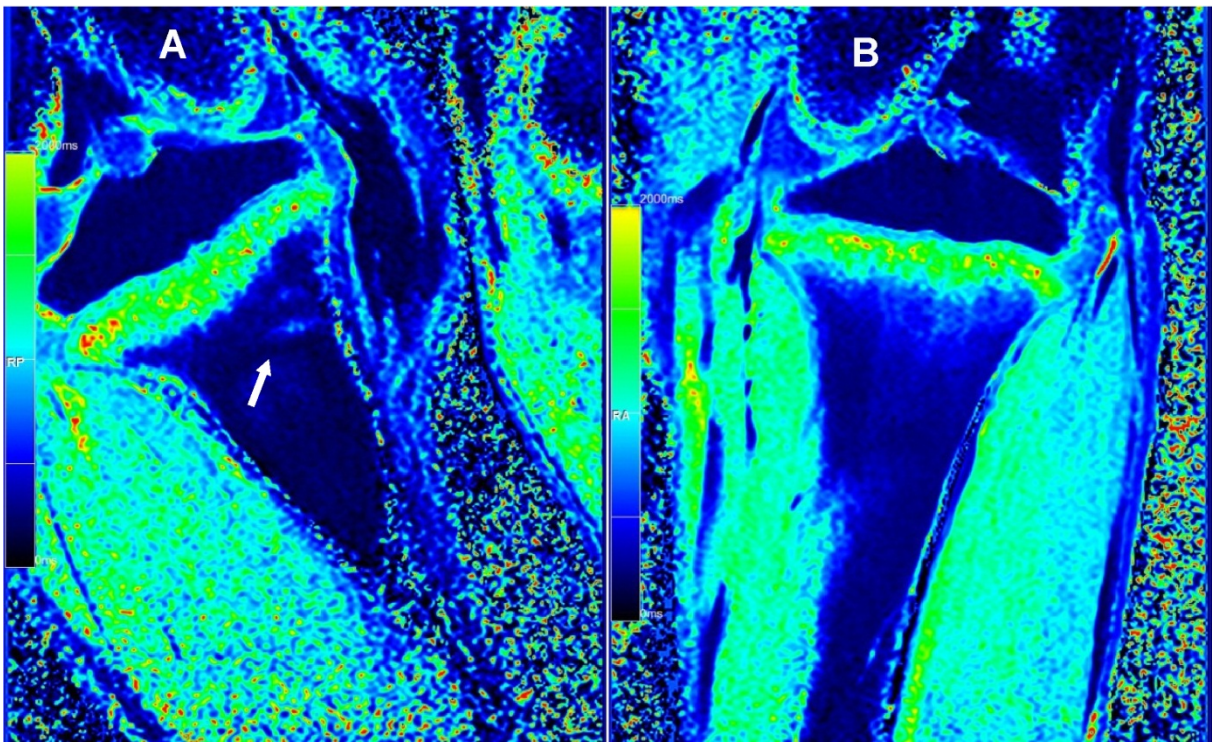

Figure 16: 15 weeks. T1 MR images (A = tension band plating and B = control) 5 weeks after removal of implants. White arrow marks trace after metaphyseal screw.

The physis was evaluated on T1 and T2 images to detect injuries to the growth plate. No damage to cartilage tissue or bony bridges was observed in any of the treated animals.

Table 5. Mean (ranges) values of interphyseal distance (mm) around on T1 whole tibia MRI.

	Temporary epiphysiodesis (n=5)	Control (n=5)	P-value
Week 0	110.3 (106.2 – 116.1)	110.0 (105.8 – 116.2)	0.5657
Week 10	127.4 (123.5 – 133.4)	138.5 (134.8 – 141.5)	0.0005
Week 15	138.8 (135.3 – 141.8)	148.1 (143.8 – 152.0)	0.0002

Table 6. Mean (ranges) pixel values from ROI's on water estimation T1 weighted MRI.

	Temporary epiphysiodesis (n=5)	Control (n=5)	P-value
Week 0	1106 (979 – 1236)	1135 (1055 – 1203)	0.5792
Week 10	502 (380 – 645)	989 (772 – 1236)	0.0021
Week 15	896 (662 – 1172)	764 (642 – 836)	0.1088

Paper III: No superiority of tension band plating compared to stapling. A randomized clinical trial on treatment of idiopathic genu valgum

The time needed to correct IGV deformity using hemiepiphysiodesis was evaluated in 26 children included in a RCT. The included children were randomly allocated to either stapling (Figure 17) or tension band plating (Figure 18) hemiepiphysiodesis. Treatment time was recorded and parameters on long standing x-rays were measured. Using the visual analog scale (VAS) pain score was documented for the first 72 hours postoperatively. Parents recorded analgesics taken after surgery. One child did not receive the intended treatment after allocation. 5 children were excluded from the analysis because of misclassification (trauma, previous malignant disease and unilateral condition) or because they reached skeletal maturity before the deformity was corrected. At follow up 20 children were eligible for analysis. Details of patient flow in Figure 19. They all achieved full correction of the genu valgum deformity. The two groups were compared using Students t-tests. The groups differed regarding gender of the operated children as more girls were allocated to tension band plating and more boys were allocated to stapling. Time to correct deformity did not differ between stapling and tension band plating (Table 8). The effect size established as Cohen's delta ((349-340)/120) is 0.075. No differences were

found between groups in relation to age, treatment time, intermalleolar distance, and measured radiographic values (LDFA, MPTA and MAD) on long standing x-rays. VAS scoring results were obtained every 12 hours starting on the day of surgery and the following 4 days (Appendix 2). When comparing these observations no differences were found between children operated with tension band plating or staples. Postoperative consumption of analgesics (paracetamol, ibuprofen, codeine and morphine) was registered on the day of surgery and continued for 3 days (Appendix 3). Consumption of analgesics did not differ between groups. One child operated with tension band plating experienced rebound growth. The child had a new hemiepiphysiodesis of the distal femoral physes performed.

Table 7. Demographics on children included in the study. CI marks 95% confidence interval.

	Tension band plating	Stapling	P-value
Children	n = 10	n = 10	
Gender (m/f)	3/7	8/2	0.02
Age (years)	10.3 (CI 8.9-11.7)	11 (CI 9.4-12.5)	0.44

Table 8. Treatment time and measurements of IM distance. CI marks 95% confidence interval.

	Tension band plating	Stapling	P-value
Treatment time (days)	340 (CI 286 - 394)	349 (CI 263 - 435)	0.84
Preoperative IM (mm)	95 (CI 78 - 111)	92 (CI 82-102)	0.71
Final IM (mm)	-2 (CI -6 – 3)	-3 (CI -8 – 2)	0.57

Table 9. Radiographic measurements on long standing x-rays. Mean values between left and right side are given. CI marks 95% confidence interval. Negative MAD values describe lateral deviation of the mechanical axis (valgus) and positive values medial deviation of the mechanical axis (varus).

	Tension band plating	Stapling	P-value
Before surgery			
LDFA (dgr)	85.5 (CI 83.9 – 87.0)	85.7 (CI 84.2 – 87.2)	0.79
MPTA (dgr)	89.8 (CI 87.9 – 91.7)	90 (CI 88.5 – 91.4)	0.89
MAD (mm)	-13 (CI -17.6 – (-8.4))	-12.2 (CI -19.9 – (-4.5))	0.84
After surgery			
LDFA (dgr)	92.4 (CI 89.5 – 95.3)	94 (CI 91.5 – 96.4)	0.37
MPTA (dgr)	90.3. (CI 87.8 – 96)	91.9 (CI 90.5 – 93.3)	0.20
MAD (mm)	9.5 (CI 3.4 – 15.4)	9.5 (CI 1.2 – 17.8)	1

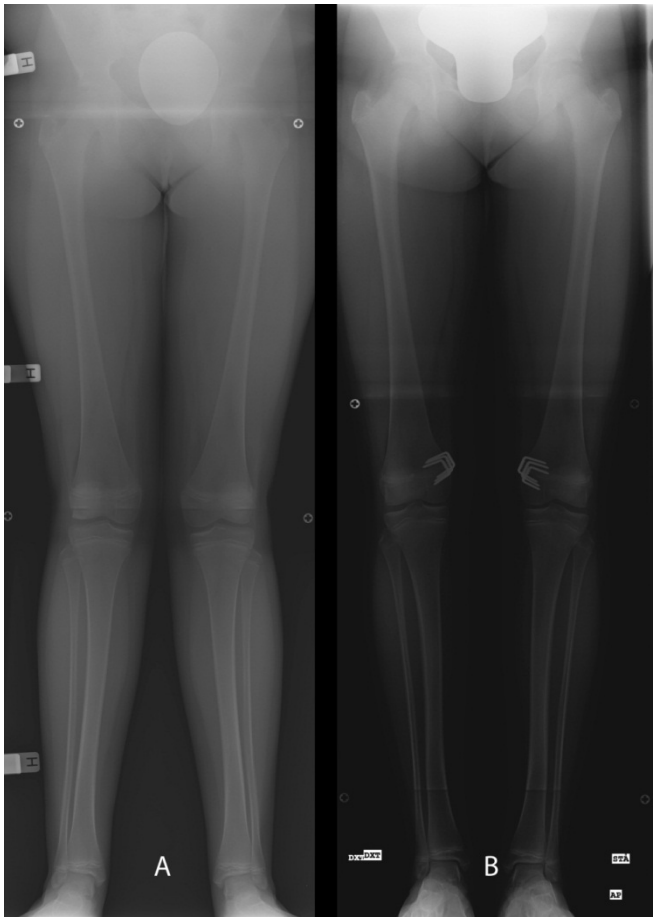

Figure 17: A showing genu valgum prior to medial stapling of the distal femoral physes. B is showing correction of genu valgum before removal of implants.

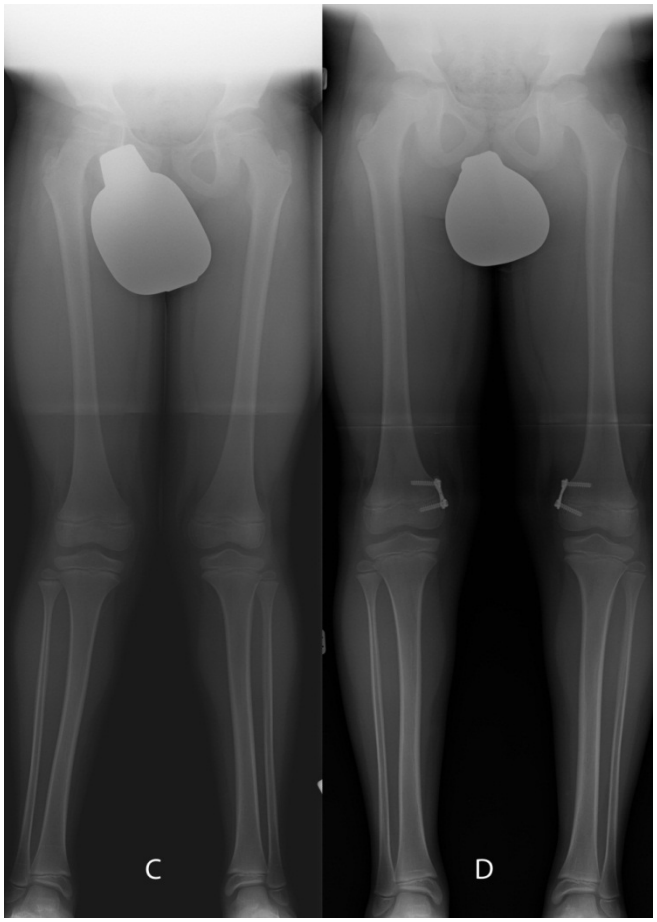

Figure 18: C showing genu valgum prior to medial hemiepiphysiodesis of the distal femoral physes using the tension band plating technique. D is showing correction of genu valgum before removal of implants.

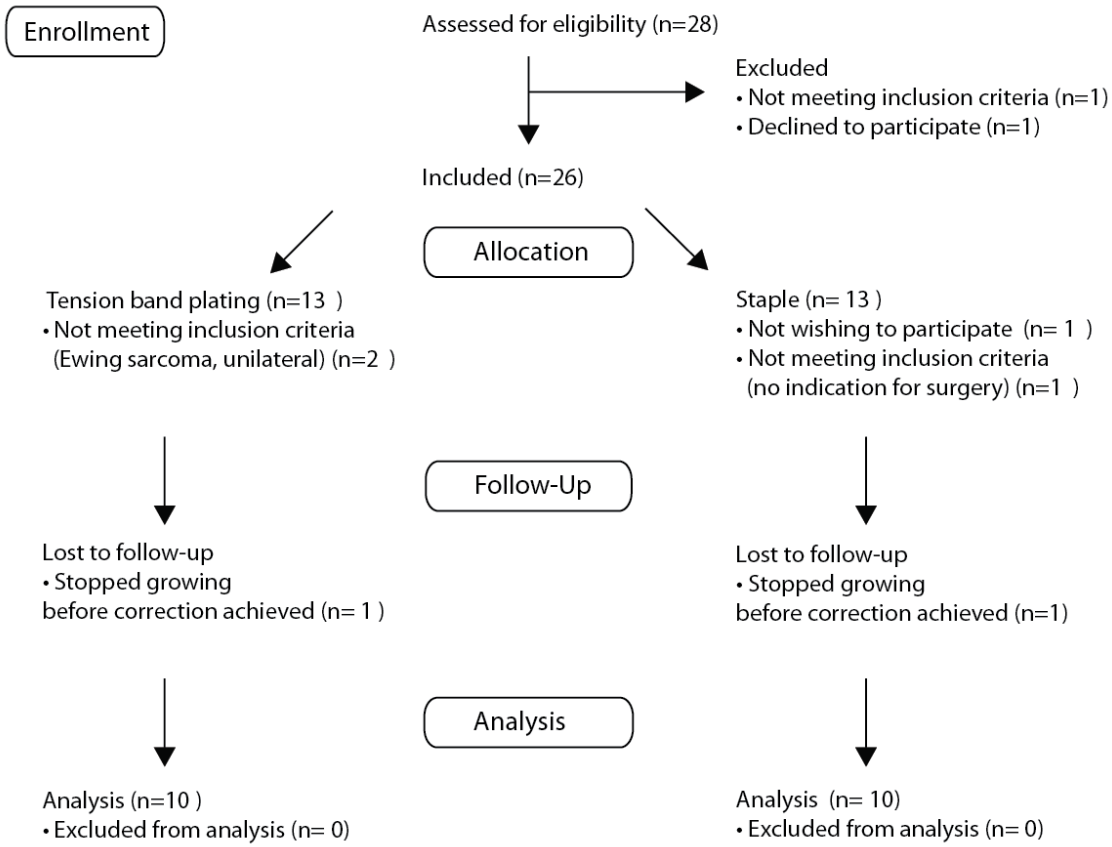

Figure 19: Consort 2010 Flowchart.

Discussion

This thesis focuses on different aspects on the use of the tension band plating technique. The first part addresses the biological response to hemiepiphysiodesis using stapling and tension band plating technique. This was evaluated using a randomised paired setup in a porcine animal model (Paper I). No differences were found between stapling and tension band plating in histomorphometric parameters in samples from tibial growth plate.

In the primary effect group (A) the cartilage growth plate appear narrow (mean height 0.56 mm) whereas in the delayed response group (B) the cartilage growth plate is nearly 4 times higher. Furthermore areas with disorganised cartilage tissue were almost entirely found in samples from animals in the delayed response group. Disorganised cartilage tissue were found in 7/8 growth plates treated with staples and 6/8 growth plates treated with tension band plating technique. Growth plate morphology after hemiepiphysiodesis using staples have previously been studied in a porcine model by Karbowski et al (80, 81). After 4-5 days of stapling they found deviation from the normal axial arrangement of the cell columns of chondrocytes in the physis. Prolonged treatment with staples resulted in splintering of hypertrophic chondrocytes in to the metaphysis and formation of a coarse like structure in the metaphysis with horizontally aligned trabeculae. Furthermore bony bridges were observed 4 months after stapling (81). Correspondingly in Paper I areas with disorganization of chondrocytes were found but interestingly it was primarily observed in the delayed response group. In Paper I, nearly all cartilage tissue examined from group A showed columnar arrangement of chondrocytes even though the animals had been treated for 9 weeks with hemiepiphysiodesis. One reason that columnar arrangement of chondrocytes appeared to be intact in the primary effect group could be related to differences in the animal model. The animals in Paper I had implants removed after 9 weeks in comparison to the study by Karbowski where animals were followed for up to 17 weeks (80, 81). Exact information on the size of the animals used in this study is unknown apart from them being 10 weeks old at the beginning of the experiment. Because weight gain corresponds to growth in animals, the lack of information on this matter makes it difficult to compare the two studies with Paper I. The animals included in Paper I had a mean weight of 38.9 kg at the beginning of the experiment and reaching 76.7 kg 9 weeks later indicating a substantial growth took place during the study period. In the work by Karbowski no tissue was examined after implant removal as their study did not include animals treated such as in group B. In another animal study rabbit lateral proximal tibia were allocated to either stapling, tension band plating, sham surgery or no surgery (98). Interestingly staple hemiepiphysiodesis seemed to produce a larger valgus deformity when compared to the tension band plating technique. Staple migration was on the contrary observed after 2 weeks of treatment with no cases of implant related failure in the tension band plating group. No results from the histological analysis were reported apart from the growth plate appearing disturbed between the staple legs. Only tissue from two animals was examined. In another study on rabbits stapling and tension band plating was applied to the lateral

distal femur and faster creation of valgus angulation using staples was observed (100). Furthermore better grasp in bone was reported for the implants used for tension band plating. Longitudinal growth of the treated femurs differed as the use of staples was correlated with overall shorter femoral bones. In their histological analysis cellular disorganisation was reported around implants in 9 preparations from a total of 34 femurs. No differences were found between implant types. Implant related injuries to the growth plate were not observed. Screw length apparently does not influence the rate of creation a deformity but again the tension band plating technique was reported to be more efficient than stapling (102). In all these three studies on rabbits custom made implants were used for the tension band plating group as commercial implants were not properly sized (98, 100, 102). Two porcine animal studies have compared stapling with tension band plating applied to medial proximal tibia in paired setups similar to group A in Paper I (99, 101). Larger changes in radiographic angles were measured for tension band plating implants compared to stapling. Furthermore the distance between medial tibial cortex and the implants were measured. This distance became significantly increased for staples during the study period indicating that staples had started pulling out of the bone. However no true implant failure was noted (99). In this study only one staple was applied spanning the growth plate and Blount has previously argued for the use of 3 staples in clinical practice to reduce variation in outcome after hemiepiphysiodesis and increase the efficiency of the procedure. In the other porcine study, medial hemiepiphysiodesis induced similar varus angulation but the degree of angulation created was larger using the tension band plating technique apparently because several staples were dragged through the growth plate (101). Again only one staple was used at each treated physis. Both these porcine studies indicate that tension band plating is a more efficient technique for guided growth but the use of single staples should be taken into account as this potentially reduces the effect of stapling and probably increases the risk for implant failure. Histology was not evaluated in these studies and the question of rebound growth after removal of implants was not addressed. In Paper I both the primary effect (A) and the delayed response (B) were investigated using the same standardized setup with animals from the same population. Because of this it seems unlikely that the changes observed are not the result of the intervention. This indicates an equal biological response in the physis to stapling and tension band plating. It is unknown how growth plate cartilage from the lateral side was affected as tissue was not sampled from this area. Furthermore quantification of growth plate morphology may not be sensitive enough to detect differences between the two techniques. The observed variation in results on growth plate morphology is probably related to biological variation but error related to the sampling technique might have contributed to bigger variation in data too. It is a limitation to the study that radiological follow up data are not available for correlation with the histological results. It is also possible the results would have differed if animals had been followed for a longer period. It cannot be ruled out that a type II error have occurred and that the study is underpowered. However, it is

believed that minor differences found in larger studies will be of limited interest for clinical practice.

The second part of the thesis dealt with the use of the tension band plating technique to perform a temporary epiphysiodesis and thereby control long bone growth in a porcine animal model (Paper II). This method has the potential to change current treatment of LLD as timing of the procedure may not become as important as it is now. Using tension band plating technique a temporary epiphysiodesis was obtained in the treated proximal tibia in all animals. Mean interphyseal distance was significantly longer in control tibiae compared to those subjected to temporary epiphysiodesis. This difference in interphyseal length was still evident 5 weeks after removal of implants. No hardware failure or loosening of implants took place, and rebound growth was not observed after removal of implants. Five weeks of follow-up is a short period though. More time could be needed to investigate the question of possible rebound growth as the physis may need more time to respond with rebound growth after temporary growth arrest. The experimental model was basically the same as in Paper I. Longitudinal bone growth is probably small compared to other species such as sheep, goat and dog. This is a disadvantage by using the porcine model in a study on treatment of LLD, because the growth velocity in porcine tibia makes it difficult to create larger differences in bone length after temporary growth control. Therefore for instance the sheep or goat could have been a useful model as they potentially have faster longitudinal bone growth. The results might therefore be limited by the choice of animal model and may not readily be transferred into clinical practice where between 2 and 5 cm of LLD commonly needs to be equalized. Growth did not stop completely after application of tension band plating. Continued growth at the physis in the proximal tibia seems unlikely as implant failure or pull out was not observed. Based on a clinical radiostereometric study on the effect of permanent epiphysiodesis some remaining growth in the arrested physis can be expected (154). The observed increase in interphyseal distance during temporary epiphysiodesis is still most likely the result of growth in the distal tibia which is believed to contribute around 50 % of the overall growth in the human tibia. The exact contribution of the distal tibial physis to bone growth in pigs is unknown. Documentation of safety and efficiency of temporary epiphysiodesis is limited to retrospective clinical papers and only one experimental study (76, 104, 155). One study report that temporary epiphysiodesis with staples in the distal femur appear to be a safe practice but staples placed bilaterally over the proximal tibia risked inducing a angulating deformity (155). Also loosening of staples overall appear to be a problem (76). The effect of bilateral stapling of the proximal tibia has been investigated in an animal study on rabbits (104). Prolonged stapling seems to induce irreversible growth arrest. In 6/10 animals irreversible growth arrest was observed but the growth plate still appeared to be in continuity and no bony bridges were seen. Prolonged temporary epiphysiodesis using implants might therefore lead to permanent growth arrest. In clinical practice most surgeons stick to the two year rule that states it is safe to leave staples over a physis for two years in a growing child. This rule origin from a 1949 paper by Blount who cites a personal, non-published communication with Phemister

(68). In a previous experimental study on rabbits MRI was used to investigate the effect of epiphysiodesis on the growth plate and surrounding bone (129). Assessing metaphyseal water content and correlating it to bone growth has not previously been reported in the literature. In paper II a modern clinical MR scanner were used to visualize the effect of temporary epiphysiodesis with tension band plating implants. This was made possible as MRI was performed either before surgery, after hardware removal, or at the end of the study period. Using short echo time T1 sequences, changes in metaphyseal signal intensity were observed that corresponded to the induced growth arrest. These changes disappeared 5 weeks after removal of implants. Mean values from metaphyseal T1 ROI's appear to correlate with changes in growth in the treated physis. However, this way of assessing MRI information has not been published before and more studies are needed to validate the proposed correlation between metaphyseal water content and bone growth. Based on the findings in Paper II it is believed that water content measurements potentially can aid with detecting growth disturbances. With the introduction of this use of the tension band plating technique in clinical practice it could be speculated that correction of LLD with temporary epiphysiodesis can be performed in a safe manner at all ages during growth.

The tension band plating technique using eight-Plates or similar implants has gained widespread popularity, but evidence supporting superiority of the use of this technique instead of stapling is lacking. In a RCT stapling was compared with the tension band plating technique (Paper III). No significant differences between the two techniques were found in time to correct deformity, intermalleolar distance, and measurements on long standing x-rays. The effect size of 0.075 in relation to treatment time is small, which might indicate that the study is underpowered. However a 30% faster correction rate as previously reported with tension band plating seems unlikely given the present data (2). In Paper III data indicate a rather similar effect of tension band plating and stapling in relation to correction of IGV deformity in growing children. The results might have been influenced by gender specific issues. More girls were operated with tension band plating technique in comparison to boys where staples were used more common. It is unknown if the response to hemiepiphysiodesis differs between genders. The use of tension band plating for guided growth has been the subject of several recent clinical papers (2, 85-88, 156, 157). The reported treatment time and rate of correction in Paper III is quite similar to results published in recent retrospective studies on the use of tension band plating. Faster correction was initially reported in one retrospective study when using tension band plating compared to stapling (2) (77). On the contrary does time to correct deformity appear to be equal when comparing tension band plating and stapling in other papers (86, 88, 156, 157). The tension band plating technique does overall appear to be safe, and in favour for tension band plating is short operating time which was documented in a recent paper (157). However, complications to the tension band plating technique has been published, and are most often associated with treatment of the pathological physis like Blount's disease and skeletal dysplasia

(90, 91). The complication rate has been reported as equal between staples and tension band plating in two previous studies (86, 157).
Earlier studies on stapling however, have reported a much lower rate of satisfying results. Implant failure with staple extrusion or breakage was observed in around 10% of the treated physes and correction was only achieved in 80 - 85% of the cases (70-77). Another paper report staple loosening or dislocation in as many as 26% of procedures in the distal femur and 35% in the proximal tibia (76). Furthermore, implant loosening was much more common in children operated before the age of 8 years. Some of these papers are historical now and the rate of complications after stapling is probably lower today based on the reported outcome in newer studies comparing stapling and tension band plating (86, 88, 156, 157). This may be attributed to improved implants, learning curve or better selection of patients.
A self-reported knee scoring system would have been valuable for Paper III but unfortunately no such score has been developed for paediatric use. In the beginning of the study a scoring system freely available on the web was used, but it was developed for use with adult patients with degenerative knee joint disease. The use of this scoring system was abolished during the study. The only validated PRO scoring system specifically designed to address lower limb disorders in children is the OxFAQ as described previously (149). VAS score was registered after index surgery and no differences were found between groups in relation to VAS score. The VAS score can be used to measure a variety of clinical phenomena (158). Measurements of acute pain have been performed in at least 30 years and are in general considered valid (159). Use of the VAS score has also previously been used to measure pain in children (146, 147). In measurements of pain a line of at least 10 cm is significantly less variable than a line of 5 cm (160). As a line of 8 cm was used in Paper 3 it must be taken into account that the length of the line might have contributed to increased variation in measurements and thereby decreased the ability to detect changes between groups. Consumption of analgesics (paracetamol, ibuprofen, codeine and morphine) was registered on the day of surgery and the following 3 days. No differences were detected between groups. That the overall outcome of stapling and tension band plating today appear equal may be related to a quite identical biological effect of both techniques despite the theoretical advantage in favour of tension band plating. The study is weakened by the small number of included patients but is the first reported results from a randomized study. The results can be included in future systematic reviews on this subject. Larger clinical trials can be conducted on this matter but smaller differences found in larger studies will probably be of little clinical significance. The proposed theoretical advantage of tension band plating compared to the stapling technique is probably of minor importance.

Conclusions

Equal growth plate response to stapling and tension band plating is indicated by histomorphometric results from a porcine animal study. Both types of implants apply compression to the growth plate. Height of the growth plate was decreased in primary effect group (A) compared to the delayed response group (B). Furthermore, disorganized cartilage tissue was found in the majority of sampled tissue 5 weeks after removal of implants (B).

Tension band plating can be used for temporary epiphysiodesis, and growth seemingly resumes after removal of implants. Rebound growth was not observed in this study, but might be visible with longer follow up after removal of hardware. Careful timing of epiphysiodesis may not be as crucial, and indications for treatment of LLD could be changing.

The distribution of metaphyseal water content on MRI appear to correlate to growth activity in porcine metaphyseal bone. Using this technique it may be possible to detect disturbances in bone growth in children.

The RCT showed no difference between stapling and tension band plating for correction of IGV in relation to treatment time, intermalleolar distance, measurements on radiographs, pain, consumption of analgesics, or complications (none observed). The theoretical advantage of tension band plating is probably of minor importance in clinical practice. The tension band plating technique has none the less proven useful for guided growth and have a number of advantages including ease of removal, shorter operating time and a possible lower complication rate.

Perspectives and future research

Angulating deformities in the lower limbs are common conditions in paediatric orthopaedic practice. Guided growth using stapling and tension band plating is usually considered first choice of treatment if intervention is needed. Stapling and tension band plating seem to give the same predictable and overall good result in relation to IGV. It is however more unclear what the optimal treatment is in relation to angulating deformities with background in the pathological physis (Ricketts, Blounts etc.).

Temporary epiphysiodesis can potentially be an important part of treatment of LLD as timing of the procedure may not become as important as it is now. The animal model used to study this subject has certain limitations and a prospective clinical cohort study (approved by the Central Denmark Region Committee on Biomedical Research Ethics Sagsnr. 1-10-72-456-12) is scheduled to begin inclusion of children with LLD from October 2012.

Rebound growth is known from clinical practice and can lead to unpredictable results after guided growth. New experimental and clinical studies will be initiated to look into this matter.

Imaging may be become more important in future paediatric orthopaedic practice and MRI has certain advantages because exposure to radiation is avoided. More studies are needed to validate the relationship between measurements of metaphyseal water content on MRI and bone growth.

Little is known about the long term consequences of having guided growth performed in childhood. Future studies should address individuals that have been treated with guided growth in childhood.

References

1. Stevens P. Guided growth: 1933 to the present. *Strategies in Trauma and Limb Reconstruction* 2006; 1(1):29-35.

2. Stevens PM. Guided growth for angular correction: a preliminary series using a tension band plate. *J Pediatr Orthop* 2007; 27(3):253-259.

3. Andry N: L'orthopédie, ou, L'art de prevenir et de corriger dans les enfans les difformites du corps. Paris, Alix, 1741.

4. Eastwood DM, Sanghrajka AP. Guided growth: Recent advances in a deep-rooted concept. *J Bone Joint Surg Br* 2011; 93-B(1):12-18.

5. Goldman V, Green DW. Advances in growth plate modulation for lower extremity malalignment (knock knees and bow legs). *Curr Opin Pediatr* 2010; 22(1):47-53.

6. Saran N, Rathjen KE. Guided Growth for the Correction of Pediatric Lower Limb Angular Deformity. *J Am Acad Orthop Surg* 2010; 18(9):528-536.

7. Geneser F, Dørup J, Schacht M: Histologi. Copenhagen, Gyldendal Akademisk, 2002.

8. Nuttall JD, Brumfield LK, Fazzalari NL et al. Histomorphometric analysis of the tibial growth plate in a feline model of mucopolysaccharidosis type VI. *Calcif Tissue Int* 1999; 65(1):47-52.

9. Abad V, Meyers JL, Weise M et al. The role of the resting zone in growth plate chondrogenesis. *Endocrinology* 2002; 143(5):1851-1857.

10. Anderson HC. Vesicles associated with calcification in the matrix of epiphyseal cartilage. *J Cell Biol* 1969; 41(1):59-72.

11. Bronner F, Farch-Carson MC, Roach HI: Bone and Development; Topics in Bone Biology. London, Springer-Verlag, 2010.

12. Bush PG, Hall AC, Macnicol MF. New insights into function of the growth plate: clinical observations, chondrocyte enlargement and a possible role for membrane transporters. *J Bone Joint Surg Br* 2008; 90(12):1541-1547.

13. Limpaphayom N, Prasongchin P. Surgical Technique: Lower Limb-length Equalization by Periosteal Stripping and Periosteal Division. *Clin Orthop Relat Res* 2011.

14. Al-Aubaidi Z, Lundgaard B. [Genu valgum after proximal metaphyseal tibial fracture in children]. *Ugeskr Laeger* 2011; 173(25):1799-1801.

15. Engel GM, Staheli LT. The natural history of torsion and other factors influencing gait in childhood. A study of the angle of gait, tibial torsion, knee angle, hip rotation, and development of the arch in normal children. *Clin Orthop Relat Res* 1974; (99):12-17.

16. MacMahon EB, Carmines DV, Irani RN. Physiologic bowing in children: an analysis of the pendulum mechanism. *J Pediatr Orthop B* 1995; 4(1):100-105.

17. Saini U, Bali K, Sheth B et al. Normal development of the knee angle in healthy Indian children: a clinical study of 215 children. *Journal of Children's Orthopaedics* 2010; 4(6):579-586.

18. Arazi M, Ogun TC, Memik R. Normal development of the tibiofemoral angle in children: a clinical study of 590 normal subjects from 3 to 17 years of age. *J Pediatr Orthop* 2001; 21(2):264-267.

19. Heath CH, Staheli LT. Normal limits of knee angle in white children--genu varum and genu valgum. *J Pediatr Orthop* 1993; 13(2):259-262.

20. Sharrard WJ. Knock knees and bow legs. *Br Med J* 1976; 1(6013):826-827.

21. Fabry G. Clinical practice. Static, axial, and rotational deformities of the lower extremities in children. *Eur J Pediatr* 2010; 169(5):529-534.

22. White KK. Orthopaedic aspects of mucopolysaccharidoses. *Rheumatology (Oxford)* 2011; 50 Suppl 5:v26-v33.

23. Cheema JI, Grissom LE, Harcke HT. Radiographic characteristics of lower-extremity bowing in children. *Radiographics* 2003; 23(4):871-880.

24. Scott AC. Treatment of infantile blount disease with lateral tension band plating. *J Pediatr Orthop* 2012; 32(1):29-34.

25. Rush WA, Steiner HA. A study of lower extremity length inequality. *Am J Roentgenol Radium Ther* 1946; 56(5):616-623.

26. Subotnick SI. Limb length discrepancies of the lower extremity (the short leg syndrome). *J Orthop Sports Phys Ther* 1981; 3(1):11-16.

27. Woerman AL, Binder-Macleod SA. Leg length discrepancy assessment: accuracy and precision in five clinical methods of evaluation*. *J Orthop Sports Phys Ther* 1984; 5(5):230-239.

28. Guichet JM, Spivak JM, Trouilloud P, Grammont PM. Lower limb-length discrepancy. An epidemiologic study. *Clin Orthop Relat Res* 1991; (272):235-241.

29. Kujala UM, Friberg O, Aalto T et al. Lower limb asymmetry and patellofemoral joint incongruence in the etiology of knee exertion injuries in athletes. *Int J Sports Med* 1987; 8(3):214-220.

30. Gofton JP. Persistent low back pain and leg length disparity. *J Rheumatol* 1985; 12(4):747-750.

31. Grundy PF, Roberts CJ. Does unequal leg length cause back pain? A case-control study. *Lancet* 1984; 2(8397):256-258.

32. Soukka A, Alaranta H, Tallroth K, Heliovaara M. Leg-length inequality in people of working age. The association between mild inequality and low-back pain is questionable. *Spine (Phila Pa 1976)* 1991; 16(4):429-431.

33. Mahar RK, Kirby RL, MacLeod DA. Simulated leg-length discrepancy: its effect on mean center-of-pressure position and postural sway. *Arch Phys Med Rehabil* 1985; 66(12):822-824.

34. Murrell P, Cornwall MW, Doucet SK. Leg-length discrepancy: effect on the amplitude of postural sway. *Arch Phys Med Rehabil* 1991; 72(9):646-648.

35. Mekhail AO, Abraham E, Gruber B, Gonzalez M. Bone transport in the management of posttraumatic bone defects in the lower extremity. *J Trauma* 2004; 56(2):368-378.

36. Vitale MA, Choe JC, Sesko AM et al. The effect of limb length discrepancy on health-related quality of life: is the '2 cm rule' appropriate? *J Pediatr Orthop B* 2006; 15(1):1-5.

37. Wolff J: Das Gesetz der Transformation der Knochen. Berlin, Hirschwald, 1892.

38. Hueter C. Anatomische Studien An Den Extremitaetengelenken Neugeborener Und Erwacbsener. *Virkows Archiv Patti Anat Physiol* 1862; (25):572-599.

39. Volkmann R. Chirurgische Erfahrungen über Knochenverbiegung und Knochenwachstum. *Virchows Archiv* 1862; (24):512-540.

40. Volkmann R: Die Krankheiten der Bewegungsorgane in Handbuch der algemeinen und speciellen Chirurgie. Vol 2 ed, Stuttgart, 1865.

41. Frost H. A chondral modeling theory. *Calcified Tissue International* 1979; 28(1):181-200.

42. Stokes IA, Aronsson DD, Dimock AN et al. Endochondral growth in growth plates of three species at two anatomical locations modulated by mechanical compression and tension. *J Orthop Res* 2006; 24(6):1327-1334.

43. Ohashi N, Robling AG, Burr DB, Turner CH. The effects of dynamic axial loading on the rat growth plate. *J Bone Miner Res* 2002; 17(2):284-292.

44. Akyuz E, Braun JT, Brown NA, Bachus KN. Static versus dynamic loading in the mechanical modulation of vertebral growth. *Spine (Phila Pa 1976)* 2006; 31(25):E952-E958.

45. Niehoff A, Kersting UG, Zaucke F et al. Adaptation of mechanical, morphological, and biochemical properties of the rat growth plate to dose-dependent voluntary exercise. *Bone* 2004; 35(4):899-908.

46. De SL, Claessens A, Lefevre J, Beunen G. Gymnast wrist: an epidemiologic survey of ulnar variance and stress changes of the radial physis in elite female gymnasts. *Am J Sports Med* 1994; 22(6):846-850.

47. Caine D, Howe W, Ross W, Bergman G. Does repetitive physical loading inhibit radial growth in female gymnasts? *Clin J Sport Med* 1997; 7(4):302-308.

48. Ponseti IV, Campos J. Observations on pathogenesis and treatment of congenital clubfoot. *Clin Orthop Relat Res* 1972; 84:50-60.

49. Ponseti IV. Treatment of congenital club foot. *J Bone Joint Surg Am* 1992; 74(3):448-454.

50. Aurell Y, Andriesse H, Johansson A, Jonsson K. Ultrasound assessment of early clubfoot treatment: a comparison of the Ponseti method and a modified Copenhagen method. *J Pediatr Orthop B* 2005; 14(5):347-357.

51. Pirani S, Zeznik L, Hodges D. Magnetic resonance imaging study of the congenital clubfoot treated with the Ponseti method. *J Pediatr Orthop* 2001; 21(6):719-726.

52. Ponseti IV. Growth and development of the acetabulum in the normal child. Anatomical, histological, and roentgenographic studies. *J Bone Joint Surg Am* 1978; 60(5):575-585.

53. Pavlik A. The functional method of treatment using a harness with stirrups as the primary method of conservative therapy for infants with congenital dislocation of the hip. 1957. *Clin Orthop Relat Res* 1992; (281):4-10.

54. Wientroub S, Green I, Terdiman R, Weissman SL. Growth and development of congenitally dislocated hips reduced in early infancy. *J Bone Joint Surg Am* 1979; 61(1):125-130.

55. Phemister DB. Operative arrestment of longitudinal growth of bones in the treatment of deformities. *J Bone Joint Surg Am* 1933; 15(1):1-15.

56. Canale ST, Russell TA, Holcomb RL. Percutaneous epiphysiodesis: experimental study and preliminary clinical results. *J Pediatr Orthop* 1986; 6(2):150-156.

57. Ramseier LE, Sukthankar A, Exner GU. Minimal invasive epiphysiodesis using a modified "Canale"-technique for correction of angular deformities and limb leg length discrepancies. *J Child Orthop* 2009; 3(1):33-37.

58. Bowen JR, Johnson WJ. Percutaneous epiphysiodesis. *Clin Orthop Relat Res* 1984; (190):170-173.

59. Horton GA, Olney BW. Epiphysiodesis of the lower extremity: results of the percutaneous technique. *J Pediatr Orthop* 1996; 16(2):180-182.

60. Metaizeau JP, Wong-Chung J, Bertrand H, Pasquier P. Percutaneous epiphysiodesis using transphyseal screws (PETS). *J Pediatr Orthop* 1998; 18(3):363-369.

61. Nouth F, Kuo LA. Percutaneous epiphysiodesis using transphyseal screws (PETS): prospective case study and review. *J Pediatr Orthop* 2004; 24(6):721-725.

62. Khoury JG, Tavares JO, McConnell S et al. Results of screw epiphysiodesis for the treatment of limb length discrepancy and angular deformity. *J Pediatr Orthop* 2007; 27(6):623-628.

63. Shin SJ, Cho TJ, Park MS et al. Angular deformity correction by asymmetrical physeal suppression in growing children: stapling versus percutaneous transphyseal screw. *J Pediatr Orthop* 2010; 30(6):588-593.

64. Ilharreborde B, Gaumetou E, Souchet P et al. Efficacy and late complications of percutaneous epiphysiodesis with transphyseal screws. *J Bone Joint Surg Br* 2012; 94(2):270-275.

65. De B, V, Moens P. Temporary hemiepiphysiodesis for idiopathic genua valga in adolescents: percutaneous transphyseal screws (PETS) versus stapling. *J Pediatr Orthop* 2008; 28(5):549-554.

66. Haas SL. Retardation of bone growth by a wire loop. *J Bone Joint Surg Am* 1945; 27(1):25-36.

67. Haas SL. Mechanical retardation of bone growth. *J Bone Joint Surg Am* 1948; 30(2):506-512.

68. Blount WP, Clarke GR. Control of bone growth by epiphyseal stapling; a preliminary report. *J Bone Joint Surg Am* 1949; 31A(3):464-478.

69. Bowen JR, Leahey JL, Zhang ZH, MacEwen GD. Partial epiphysiodesis at the knee to correct angular deformity. *Clin Orthop Relat Res* 1985; (198):184-190.

70. Brockway A, Craig WA, Cockreli BR, Jr. End-result study of sixty-two stapling operations. *J Bone Joint Surg Am* 1954; 36-A(5):1063-1070.

71. Blount WP. A mature look at epiphyseal stapling. *Clin Orthop Relat Res* 1971; 77:158-163.

72. Pistevos G, Duckworth T. The correction of genu valgum by epiphysial stapling. *J Bone Joint Surg Br* 1977; 59(1):72-76.

73. Zuege RC, Kempken TG, Blount WP. Epiphyseal stapling for angular deformity at the knee. *J Bone Joint Surg Am* 1979; 61(3):320-329.

74. Fraser RK, Dickens DR, Cole WG. Medial physeal stapling for primary and secondary genu valgum in late childhood and adolescence. *J Bone Joint Surg Br* 1995; 77(5):733-735.

75. Stevens PM, Maguire M, Dales MD, Robins AJ. Physeal stapling for idiopathic genu valgum. *J Pediatr Orthop* 1999; 19(5):645-649.

76. Raab P, Wild A, Seller K, Krauspe R. Correction of length discrepancies and angular deformities of the leg by Blount's epiphyseal stapling. *Eur J Pediatr* 2001; 160(11):668-674.

77. Courvoisier A, Eid A, Merloz P. Epiphyseal stapling of the proximal tibia for idiopathic genu valgum. *J Child Orthop* 2009; 3(3):217-221.

78. Mielke CH, Stevens PM. Hemiepiphyseal stapling for knee deformities in children younger than 10 years: a preliminary report. *J Pediatr Orthop* 1996; 16(4):423-429.

79. Goff CW. Histologic arrangements from biopsies of epiphyseal plates of children before and after stapling. Correlated with roentgenographic studies. *Am J Orthop* 1967; 9(5):87-89.

80. Karbowski A, Camps L, Matthiass HH. Metaphyseal aspects of stapling. An experimental study in pigs. *Arch Orthop Trauma Surg* 1989; 108(4):195-202.

81. Karbowski A, Camps L, Matthiass HH. Histopathological features of unilateral stapling in animal experiments. *Arch Orthop Trauma Surg* 1989; 108(6):353-358.

82. Herwig J, Schmidt A, Matthiab HH et al. Biochemical events during stapling of the proximal tibial epiphyseal plate in pigs. *Clin Orthop Relat Res* 1987; (218):283-289.

83. Jung HJ, Cho TJ, Choi IH et al. Change in effective leg length after angular deformity correction by hemiepiphyseal stapling. *Clin Orthop Surg* 2010; 2(2):85-89.

84. Guzman H, Yaszay B, Scott VP et al. Early experience with medial femoral tension band plating in idiopathic genu valgum. *J Child Orthop* 2011; 5(1):11-17.

85. Burghardt RD, Herzenberg JE, Standard SC, Paley D. Temporary hemiepiphyseal arrest using a screw and plate device to treat knee and ankle deformities in children: a preliminary report. *J Child Orthop* 2008; (2):187-197.

86. Wiemann JM, Tryon C, Szalay EA. Physeal stapling versus 8-plate hemiepiphysiodesis for guided correction of angular deformity about the knee. *J Pediatr Orthop* 2009; 29(5):481-485.

87. Ballal MS, Bruce CE, Nayagam S. Correcting genu varum and genu valgum in children by guided growth: Temporary hemiepiphysiodesis using tension band plates.. *J Bone Joint Surg Br* 2010; 92(2):273-276.

88. Burghardt RD, Herzenberg JE. Temporary hemiepiphysiodesis with the eight-Plate for angular deformities: mid-term results. *J Orthop Sci* 2010; 15(5):699-704.

89. Boero S, Michelis MB, Riganti S. Use of the eight-Plate for angular correction of knee deformities due to idiopathic and pathologic physis: initiating treatment according to etiology. *J Child Orthop* 2011; 5(3):209-216.

90. Schroerlucke S, Bertrand S, Clapp J et al. Failure of Orthofix eight-Plate for the Treatment of Blount Disease. *J Pediatr Orthop* 2009; 29(1):57-60.

91. Burghardt RD, Specht SC, Herzenberg JE. Mechanical Failures of eight-Plate Guided Growth System for Temporary Hemiepiphysiodesis. *J Pediatr Orthop* 2010; 30(6):594-597.

92. Oto M, Yilmaz G, Bowen JR et al. Adolescent Blount disease in obese children treated by eight-plate hemiepiphysiodesis. *Eklem Hastalik Cerrahisi* 2012; 23(1):20-24.

93. Klatt J, Stevens PM. Guided growth for fixed knee flexion deformity. *J Pediatr Orthop* 2008; 28(6):626-631.

94. Al-Aubaidi Z, Engell V, Lundgaard B. [Stress fracture following femoral epiphysiodesis]. *Ugeskr Laeger* 2010; 172(41):2847-2848.

95. Al-Aubaidi Z, Lundgaard B, Pedersen NW. Anterior distal tibial epiphysiodesis for the treatment of recurrent equinus deformity after surgical treatment of clubfeet. *J Pediatr Orthop* 2011; 31(6):716-720.

96. Oda JE, Thacker MM. Distal tibial physeal bridge: a complication from a tension band plate and screw construct. Report of a case. *J Pediatr Orthop B* 2011 Dec 9. [Epub ahead of print].

97. Stitgen A, Garrels K, Kobayashi H et al. Biomechanical comparison between 2 guided-growth constructs. *J Pediatr Orthop* 2012; 32(2):206-209.

98. Mast N, Brown NA, Brown C, Stevens PM. Validation of a genu valgum model in a rabbit hind limb. *J Pediatr Orthop* 2008; 28(3):375-380.

99. Kanellopoulos AD, Mavrogenis AF, Dovris D et al. Temporary hemiepiphysiodesis with blount staples and eight-plates in pigs. *Orthopedics* 2011; 34(4).

100. Goyeneche RA, Primomo CE, Lambert N, Miscione H. Correction of bone angular deformities: experimental analysis of staples versus 8-plate. *J Pediatr Orthop* 2009; 29(7):736-740.

101. Burghardt RD, Kanellopoulos AD, Herzenberg JE. Hemiepiphyseal arrest in a porcine model. *J Pediatr Orthop* 2011; 31(4):e25-e29.

102. Raluy-Collado D, Sanpera I, Jr., Frontera-Juan G et al. Screw length in the guided growth method. *Arch Orthop Trauma Surg* 2012; 132(12):1711-1715.

103. Stokes IA, Mente PL, Iatridis JC et al. Enlargement of growth plate chondrocytes modulated by sustained mechanical loading. *J Bone Joint Surg Am* 2002; 84-A(10):1842-1848.

104. Christensen NO. Growth arrest by stapling. An experimental study of longitudinal bone growth and morphology of the growth region. *Acta Orthop Scand Suppl* 1973; 3-78.

105. McCarthy JJ, Noonan KJ, Nemke B, Markel M. Guided growth of the proximal femur: a pilot study in the lamb model. *J Pediatr Orthop* 2010; 30(7):690-694.

106. Grover JP, Vanderby R, Leiferman EM et al. Mechanical behavior of the lamb growth plate in response to asymmetrical loading: a model for Blount disease. *J Pediatr Orthop* 2007; 27(5):485-492.

107. Karaharju EO, Ryoppy SA, Makinen RJ. Remodelling by asymmetrical epiphysial growth. An experimental study in dogs. *J Bone Joint Surg Br* 1976; 58(1):122-126.

108. Pearce AI, Richards RG, Milz S et al. Animal models for implant biomaterial research in bone: a review. *Eur Cell Mater* 2007; 13:1-10.

109. Swindle M: Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques. 2007.

110. Thorwarth M, Schultze-Mosgau S, Kessler P et al. Bone regeneration in osseous defects using a resorbable nanoparticular hydroxyapatite. *J Oral Maxillofac Surg* 2005; 63(11):1626-1633.

111. Raab DM, Crenshaw TD, Kimmel DB, Smith EL. A histomorphometric study of cortical bone activity during increased weight-bearing exercise. *J Bone Miner Res* 1991; 6(7):741-749.

112. Mosekilde L, Kragstrup J, Richards A. Compressive strength, ash weight, and volume of vertebral trabecular bone in experimental fluorosis in pigs. *Calcif Tissue Int* 1987; 40(6):318-322.

113. Aerssens J, Boonen S, Lowet G, Dequeker J. Interspecies differences in bone composition, density, and quality: potential implications for in vivo bone research. *Endocrinology* 1998; 139(2):663-670.

114. Mosekilde L, Weisbrode SE, Safron JA et al. Calcium-restricted ovariectomized Sinclair S-1 minipigs: an animal model of osteopenia and trabecular plate perforation. *Bone* 1993; 14(3):379-382.

115. Kragstrup J, Richards A, Fejerskov O. Effects of fluoride on cortical bone remodeling in the growing domestic pig. *Bone* 1989; 10(6):421-424.

116. Jones JK, Gill L, John M et al. Outcome analysis of surgery for Blount disease. *J Pediatr Orthop* 2009; 29(7):730-735.

117. Gundersen HJ, Bendtsen TF, Korbo L et al. Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. *APMIS* 1988; 96(5):379-394.

118. Overgaard S, Soballe K, Jorgen H, Gundersen G. Efficiency of systematic sampling in histomorphometric bone research illustrated by hydroxyapatite-coated implants: optimizing the stereological vertical-section design. *J Orthop Res* 2000; 18(2):313-321.

119. Byers S, Moore AJ, Byard RW, Fazzalari NL. Quantitative histomorphometric analysis of the human growth plate from birth to adolescence. *Bone* 2000; 27(4):495-501.

120. Gundersen HJ, Bagger P, Bendtsen TF et al. The new stereological tools: disector, fractionator, nucleator and point sampled intercepts and their use in pathological research and diagnosis. *APMIS* 1988; 96(10):857-881.

121. Slomianka L, West MJ. Estimators of the precision of stereological estimates: an example based on the CA1 pyramidal cell layer of rats. *Neuroscience* 2005; 136(3):757-767.

122. Winalski CS, Rajiah P. The evolution of articular cartilage imaging and its impact on clinical practice. *Skeletal Radiol* 2011; 40(9):1197-1222.

123. Li X, Wang R, Li Y et al. MRI characteristics and transverse relaxation time measurements in normal growing cartilage. *J Huazhong Univ Sci Technolog Med Sci* 2004; 24(4):411-413.

124. George J, Nagendran J, Azmi K. Comparison study of growth plate fusion using MRI versus plain radiographs as used in age determination for exclusion of overaged football players. *Br J Sports Med* 2012; 46(4):273-278.

125. Koff MF, Chong lR, Virtue P et al. Correlation of magnetic resonance imaging and histologic examination of physeal bars in a rabbit model. *J Pediatr Orthop* 2010; 30(8):928-935.

126. Sanchez TR, Jadhav SP, Swischuk LE. MR imaging of pediatric trauma. *Magn Reson Imaging Clin N Am* 2009; 17(3):439-50, v.

127. Kim A, Dombi E, Solomon J et al. Automated volumetric growth plate measurement using magnetic resonance imaging for monitoring skeletal toxicity in children treated on investigational drug trials. *Clin Cancer Res* 2011; 17(18):5982-5990.

128. Chung T, Jaramillo D. Normal maturing distal tibia and fibula: changes with age at MR imaging. *Radiology* 1995; 194(1):227-232.

129. Synder M, Harcke HT, Conard K, Bowen JR. Experimental epiphysiodesis: magnetic resonance imaging evaluation with histopathologic correlation. *Int Orthop* 2001; 25(6):337-342.

130. Synder M, Harcke HT, Bowen JR, Caro PA. Evaluation of physeal behavior in response to epiphyseodesis with the use of serial magnetic resonance imaging. *J Bone Joint Surg Am* 1994; 76(2):224-229.

131. Li X, Wang R, Li Y et al. Epiphyseal and physeal cartilage: normal gadolinium-enhanced MR imaging. *J Huazhong Univ Sci Technolog Med Sci* 2005; 25(2):209-211.

132. Errani C, Kreshak J, Ruggieri P et al. Imaging of bone tumors for the musculoskeletal oncologic surgeon. *Eur J Radiol* 2011; Dec 28. [Epub ahead of print].

133. Anumula S, Wehrli SL, Magland J et al. Ultra-short echo-time MRI detects changes in bone mineralization and water content in OVX rat bone in response to alendronate treatment. *Bone* 2010; 46(5):1391-1399.

134. Li X, Ma BC, Bolbos RI et al. Quantitative assessment of bone marrow edema-like lesion and overlying cartilage in knees with osteoarthritis and anterior cruciate ligament tear using MR imaging and spectroscopic imaging at 3 Tesla. *J Magn Reson Imaging* 2008; 28(2):453-461.

135. Bae WC, Chen PC, Chung CB et al. Quantitative ultrashort echo time (UTE) MRI of human cortical bone: correlation with porosity and biomechanical properties. *J Bone Miner Res* 2012; 27(4):848-857.

136. Hunt MA, Fowler PJ, Birmingham TB et al. Foot rotational effects on radiographic measures of lower limb alignment. *Can J Surg* 2006; 49(6):401-406.

137. Sanfridsson J, Ryd L, Svahn G et al. Radiographic measurement of femorotibial rotation in weight-bearing. The influence of flexion and extension in the knee on the extensor mechanism and angles of the lower extremity in a healthy population. *Acta Radiol* 2001; 42(2):207-217.

138. Guichet JM, Javed A, Russell J, Saleh M. Effect of the foot on the mechanical alignment of the lower limbs. *Clin Orthop Relat Res* 2003; (415):193-201.

139. Paley D: Principles of Deformity Correction. Springer, Verlag, 2002.

140. Sabharwal S, Zhao C, Edgar M. Lower limb alignment in children: reference values based on a full-length standing radiograph. *J Pediatr Orthop* 2008; 28(7):740-746.

141. Sabharwal S, Zhao C, McKeon JJ et al. Computed radiographic measurement of limb-length discrepancy. Full-length standing anteroposterior radiograph compared with scanogram. *J Bone Joint Surg Am* 2006; 88(10):2243-2251.

142. Moreland JR, Bassett LW, Hanker GJ. Radiographic analysis of the axial alignment of the lower extremity. *J Bone Joint Surg Am* 1987; 69(5):745-749.

143. Inan M, Jeong C, Chan G et al. Analysis of lower extremity alignment in achondroplasia: interobserver reliability and intraobserver reproducibility. *J Pediatr Orthop* 2006; 26(1):75-78.

144. Gordon JE, Chen RC, Dobbs MB et al. Interobserver and intraobserver reliability in the evaluation of mechanical axis deviation. *J Pediatr Orthop* 2009; 29(3):281-284.

145. Nowicki PD, Vanderhave KL, Farley FA et al. Reliability of digital radiographs for pediatric lower extremity alignment. *J Pediatr Orthop* 2012; 32(6):631-635.

146. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. *Ann Emerg Med* 2001; 37(1):28-31.

147. Vetter TR, Heiner EJ. Discordance between patient self-reported visual analog scale pain scores and observed pain-related behavior in older children after surgery. *J Clin Anesth* 1996; 8(5):371-375.

148. Daltroy LH, Liang MH, Fossel AH, Goldberg MJ. The POSNA pediatric musculoskeletal functional health questionnaire: report on reliability, validity, and sensitivity to change. Pediatric Outcomes Instrument Development Group. Pediatric Orthopaedic Society of North America. *J Pediatr Orthop* 1998; 18(5):561-571.

149. Morris C, Doll HA, Wainwright A et al. The Oxford ankle foot questionnaire for children: scaling, reliability and validity. *J Bone Joint Surg Br* 2008; 90(11):1451-1456.

150. Nielsen S, Ruperto N, Herlin T, Pedersen FK. The Danish version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol* 2001; 19(4 Suppl 23):S50-S54.

151. Smink JJ, Buchholz IM, Hamers N et al. Short-term glucocorticoid treatment of piglets causes changes in growth plate morphology and angiogenesis. *Osteoarthritis Cartilage* 2003; 11(12):864-871.

152. Sergerie K, LacoursiΦre MO, LθvesqueM, Villemure I. Mechanical properties of the porcine growth plate and its three zones from unconfined compression tests. *Journal of Biomechanics* 2009; 42(4):510-516.

153. Mouton PR: Principles and Practices of Unbiased Stereology: An Introduction For Bioscientists. Baltimore, Johns Hopkins University, 2002.

154. Lauge-Pedersen H, Hagglund G, Johnsson R. Radiostereometric analysis for monitoring percutaneous physiodesis. A preliminary study. *J Bone Joint Surg Br* 2006; 88(11):1502-1507.

155. Gorman TM, Vanderwerff R, Pond M et al. Mechanical axis following staple epiphysiodesis for limb-length inequality. *J Bone Joint Surg Am* 2009; 91(10):2430-2439.

156. Niethard M, Deja M, Rogalski M. [Correction of angular deformity of the knee in growing children by temporary hemiepiphyseodesis using the eight-plate]. *Z Orthop Unfall* 2010; 148(2):215-221.

157. Jelinek EM, Bittersohl B, Martiny F et al. The 8-plate versus physeal stapling for temporary hemiepiphyseodesis correcting genu valgum and genu varum: a retrospective analysis of thirty five patients. *Int Orthop* 2012; 36(3):599-605.

158. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990; 13(4):227-236.

159. Seymour RA. The use of pain scales in assessing the efficacy of analgesics in post-operative dental pain. *Eur J Clin Pharmacol* 1982; 23(5):441-444.

160. Revill SI, Robinson JO, Rosen M, Hogg MI. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; 31(9):1191-1198.

Appendices

Appendix 1. Characteristics of animals receiving sham surgery. Mean values (ranges) from each sham treated leg are given.

	Tension band plating (n=2)	Stapling (n=2)
Zone of reserve	0.23 (0.22 – 0.25)	0.24 (0.23 – 0.25)
Zone of proliferation	0.47 (0.44 – 0.51)	0.48 (0.45 – 0.52)
Zone of hypertrophy	0.29 (0.27 – 0.31)	0.24 (0.23 – 0.25)
Disorganized cartilage	0	0
Height of growth plate	757 (719 – 795)	829 (814 – 844)

Appendix 2. Postoperative pain score using VAS. Mean values (ranges) are given.

	Tension band plating	Stapling	P-value
VAS 12h	0.41 (0.05 – 0.9)	0.32 (0 – 1)	0.57
VAS 24h	0.56 (0.17 – 0.78)	0.54 (0.13 – 0.82)	0.83
VAS 36h	0.55 (0.17 – 0.9)	0.39 (0.1 – 0.93)	0.24
VAS 48h	0.38 (0.04 – 1)	0.33 (0.03 – 0.75)	0.76
VAS 60h	0.34 (0.1 – 0.81)	0.29 (0 – 0.83)	0.70
VAS 72h	0.25 (0 – 0.66)	0.30 (0 – 0.66)	0.66
VAS 84h	0.30 (0.08 – 0.84)	0.23 (0 – 0.7)	0.50
VAS 96h	0.17 (0.03 – 0.49)	0.24 (0 – 0.6)	0.47
VAS 108h	0.22 (0.01 – 0.6)	0.19 (0 – 0.69)	0.80

Appendix 3. Postoperative consumption of analgesics. Numbers indicate mean doses of analgesics taken. Mean values (ranges) are given.

		Tension band plating	Stapling	P-value
Day 0	Paracetamol	2.6 (1 – 4)	2 (0 – 3)	0.29
	NSAID	1.4 (1 – 2)	1.4 (0 – 3)	1
	Morphine	0.2 (0 - 1)	0.3 (0 – 1)	0.43
	Codeine	0.3 (0 - 2)	0.6 (0 - 3)	0.54
Day 1	Paracetamol	3.6 (3 – 4)	3.2 (2 – 4)	0.33
	NSAID	2.7 (1 – 4)	2.7 (2 – 4)	1
	Morphine	1 (0 – 3)	0.7 (0 – 2)	0.54
	Codeine	1 (0 – 4)	0.6 (0 – 3)	0.52
Day 2	Paracetamol	3.8 (2 – 4)	2.9 (1 – 4)	0.09
	NSAID	2.2 (0 – 4)	2 (0 – 4)	0.73
	Morphine	0.8 (0 – 2)	0.1 (0 – 1)	0.07
	Codeine	0.2 (0 – 2)	0.3 (0 – 2)	0.74
Day 3	Paracetamol	3 (1 – 4)	2.6 (0 – 4)	0.50
	NSAID	1.8 (0 – 3)	1.7 (0 – 4)	0.87
	Morphine	0.3 (0 – 1)	0	0.06
	Codeine	0.4 (0 – 3)	0.2 (0 – 2)	0.59

Papers I-III