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Ph.D. thesis

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Classification and current treatment principles in Early-Onset Scoliosis

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Preface and acknowledgements

This thesis includes four separate studies. It begins with a brief introduction to the subject highlighting the challenges in the treatment of early-onset scoliosis. This is followed by a description of the included study populations, study designs, methodology and statistical considerations. The results of the four studies are briefly summarized and lastly discussed in the context of the international literature. In the last section, the four studies are included in their full length. The work has been carried out at the Spine Unit, Department of Orthopaedic surgery at Rigshospitalet between 2016 and 2019.

I would like to thank all the people who have helped me throughout my work on this thesis including the staff at the Spine Unit's office. A special thanks to my supervisors **Martin Gehrchen** and **Benny Dahl** who gave me this opportunity. I must admit, I became a bit anxious at my first day at work when you told me that Benny was leaving. But **Martin** you have lifted an enormous job supervising four PhD. students, and **Benny** your encouraging enthusiasm is felt despite the long distance. I look up to the way you both approach your patients and I will miss your implied humor. Also, I would like to thank my supervisor **Thomas Andersen** especially for providing me with clinical knowledge about these patients. I owe a huge gratitude to my co-supervisor **Søren Ohrt-Nissen**. I really enjoyed the first year where we shared office discussing everything from kids over careers to football. I had the honor to help you with some of your projects and you have taught me how to write scientifically. Your sharp mind and efficient work are inspiring, and I look forward to working with you in the future. I would like to thank the other co-authors **Niklas Tøndevold**, **Sidsel Fruergaard**, **Dennis Hallager**, **Mohit Jain** and the people at Texas Children's Hospital. Thanks to **Benny and his wife Lone** for welcoming me and my family in Houston with open arms making it a memorable stay. Thanks to **Lærke Ragborg** for helping with some of the boring hard work in other studies and to **Karen Dyreborg** and **Marina Golemac** for helping me out with the DXA-scanner. A huge thanks to my dear colleagues at the office **Sidsel Fruergaard, Frederik Pitter and Tanvir Bari** for great company on travels, academic discussions and for making every day at the office joyful. Finally, I would like to thank my family and especially my wife **Anne-Cathrine**. You have taken care of our wonderful children these last busy months and your love and endless support means the world to me.

And to my dear mother: I hope you are smiling and watching from somewhere up there.

Abbreviations and concepts

AIS: Adolescent idiopathic scoliosis

APR: Annual progression rate (°/year) = (MCA @ t_2 – MCA @t_1) / (t_2 – t_1)

aBMD: areal bone mineral density

$aBMD_{age}$ Z-score: age-adjusted aBMD Z-score

$aBMD_{HAZ}$ Z-score: height-for-age adjusted aBMD Z-score

BMD: Bone mineral density

C-EOS: Classification of Early-Onset Scoliosis

Curve correction (%) = (preoperative MCA – postoperative MCA) / preoperative MCA*100

CCI: Curve correction index = (Curve correction) / Flexibility

EOS: Early-onset scoliosis

Flexibility (%) = (preoperative MCA – bending MCA)/preoperative MCA*100

FVC: Forced vital capacity (%)

LOA: Limits of agreement

MCA: Major curve angle

MCGR: Magnetically controlled growing rods

MRI: Magnetic resonance imaging

PJK: Proximal junctional kyphosis

SEM: Standard error of measurements

T1S1: Total spinal height measured in the coronal plane

T1T12: Thoracic spinal height measured in the coronal plane

Summary (English)

Early-onset scoliosis (EOS) is a heterogeneous condition ranging from mild and resolving to severe and progressive deformity. EOS can be classified according to the underlying etiology as congenital/structural, neuromuscular, syndromic or idiopathic. If left untreated, progressive EOS may result in pulmonary compromise and increased mortality. Early fusion of the thoracic spine can lead to a restrictively decreased pulmonary function. Therefore, various distraction-based techniques and implants have been developed to allow continuous growth of the spine, while trying to control the deformity. However, they require repetitive surgical procedures with high complication and infection rates. To avoid this, a magnetically control growing rod (MCGR) was recently developed, which allows non-invasive lengthening procedures while partly correcting the deformity. The technique is relatively new, and generally there is not yet consensus on the surgical indications, timing of surgery and distraction technique. Moreover, the implant-related complication rate remains high and the consequences and long-term results of the treatment are sparsely investigated. The Classification of Early-Onset Scoliosis (C-EOS) is a newly developed classification system trying to standardize research and practice within EOS. However, the content and cut-off values are to some extend based on expert consensus and the reproducibility has not been thoroughly assessed.

The objectives of this thesis were to examine reliability and accuracy of the C-EOS. Secondly, to assess the curve correction and complication rate in the MCGR treatment and the efficacy of a distraction-to-stall principle compared with a targeted distraction principle. Lastly, to investigate the bone mineral density (BMD) in the vertebrae within the instrumentation.

The first study included 60 patients in a reproducibility study of C-EOS. Agreement for etiology was substantial, however, disagreement was found regarding syndromic patients and patients with neural axis abnormalities. Reliability of major curve angle (MCA) was excellent while reliability for kyphosis and annual progression rate (APR) were lower due to larger measurement errors. The limits of agreement for APR exceeded the 10°/year increments suggested in the original paper describing the C-EOS.

The second study included 19 patients treated with MCGR. Major curve angle was reduced from 76° preoperatively to 44° postoperatively. Flexibility predicted curve correction, which was maintained throughout follow-up. The distraction-to-stall principle resulted in satisfactory lengthening with spinal height increase comparable to results published in the literature.

The third study included 39 patients treated with MCGR at two centers using either a distraction-to-stall (group 1) or a targeted distraction principle (group 2). The two groups were comparable besides a mean 18 days longer time interval between lengthening in group 2. We found no difference in achieved distraction. The only variable independently associated with greater achieved distraction within the first year was larger preoperative MCA.

The fourth study included measurements of BMD in 11 patients treated with MCGR. We found a lower BMD in vertebrae spanned by the instrumentation compared with total hip BMD and height-for-age normative values. But the results need to be verified in a longitudinal study.

In conclusion, the C-EOS is a reliable classification system for future research in EOS although minor revisions are required. MCGR effectively corrects the coronal deformity, and distraction-to-stall and targeted distraction are equivalent lengthening principles.

Summary (Danish)

Tidlig debuterende skoliose (*Engelsk: Early-Onset Scoliosis, EOS*) er en heterogen gruppe af patienter med alt fra lette og spontant remitterende til svære progredierende rygdeformiteter. EOS kan klassificeres baseret på ætiologien som enten kongenit/strukturel, neuromuskulær, syndromrelateret eller idiopatisk. Ubehandlet kan svær EOS resultere i nedsat lungefunktion og deraf øget mortalitet sammenlignet med en normalpopulation. Tidlig fusion af den thoracale rygsøjle før patienten er udvokset kan føre til restriktiv lungefunktionsnedsættelse. Derfor er der udviklet forskellige implantater og teknikker som med forlængelser muliggør vækst af rygsøjlen samtidig med at de korrigerer deformiteten. Forlængelserne kræver gentagne åbne kirurgiske procedurer med høje komplikations- og infektionsrater til følge. For at udgå dette er en magnetisk kontrolleret vækstinstrumentering (MCGR) blevet udviklet som tillader udførelse af non-invasive forlængelsesprocedurer og samtidig korrigerer rygdeformiteten. Teknikken er relativt ny og der er ingen konsensus angående indikation, timing og forlængelsesteknik. Ydermere er komplikationsraten stadig høj og der foreligger få langtidsresultater af behandlingen.

Et nyt klassifikationssystem for EOS (Classification of Early-Onset Scoliosis, C-EOS) er blevet udviklet for at standardisere forskningen og klinisk praksis for patienter med EOS. Men indholdet og cut-off værdierne er i nogen grad baseret på ekspertviden og reproducérbarheden er ikke tilstrækkeligt undersøgt.

Formålet med afhandlingen var at teste reproducérbarheden af C-EOS. At vurdere kurvekorrektion og komplikationsrate under behandlingen med MCGR og undersøge resultaterne af en forlængelse-til-stall teknik sammenlignet med en estimeret forlængelsesteknik. Og til sidst at undersøge knoglemineraltætheden (BMD) i vertebrae indenfor instrumenteringen.

Det første studie inkluderede 60 patienter i et reproducérbarhedsstudie af C-EOS. Reliabiliteten for ætiologi var god, men der var nogen uenighed mellem observatørerne for især syndrompatienter og patienter med intraspinal patologi. Reliabiliteten for major curve angle (MCA) var fremragende, men lavere for kyfose og årlig progressionsrate (APR) på grund af større måleusikkerhed. Måleusikkerheden for APR oversteg uanset ætiologi de 10°/år som C-EOS foreslår til at skelne mellem patienterne.

Studie 2 inkluderede 19 patienter opereret med MCGR. Hovedkurven blev reduceret fra 76° præoperativt til 44° postoperativt uden tab a kurvekorrektion under follow-up. Fleksibiliteten var afgørende for kurvekorrektionen. Forlængelse-til-stall princippet resulterede i tilfredsstillende højdetilvækst af columna sammenholdt med den tilgængelige litteratur.

Studie 3 inkluderede 39 patienter opereret med MCGR på to centre. Det ene center (gruppe 1) anvendte et forlængelse-til-stall princip og det andet (gruppe 2) et estimeret forlængelsesprincip. Grupperne var sammenlignelige fraset et gennemsnitlig 18 dages længere interval mellem forlængelserne i gruppe 2. Vi fandt ingen forskel i forlængelse mellem grupperne. Den eneste variabel som uafhængigt var associeret med øget forlængelse, var præoperativ kurvestørrelse.

I det sidste studie undersøgte vi i et tværsnitsstudie BMD i 11 patienter opereret med MCGR. Vi fandt en lavere BMD i vertebrae inden for instrumenteringen sammenlignet med BMD i hofteregionen og med højde og aldersjusterede værdier. Resultaterne skal dog valideres i et longitudinelt studiedesign.

Vi konkluderer at C-EOS er et pålideligt klassifikationssystem som dog kræver små justeringer. Magnetisk kontrolleret vækstinstrumentering korrigerer effektivt den koronale kurvedeformitet og forlængelse-til-stall og estimeret forlængelse er ligeværdige forlængelsesteknikker.

List of papers

I. Reproducibility of the Classification of Early-Onset Scoliosis (C-EOS)

Casper Dragsted, Søren Ohrt-Nissen, Dennis Winge Hallager, Niklas Tøndevold, Thomas Andersen, Benny Dahl, Martin Gehrchen

Accepted for publication in Spine Deformity, October 2019.

II. Use of a distraction-to-stall lengthening procedure in magnetically controlled growing rods: A single-center cohort study

Dahl B, Dragsted C, Ohrt-Nissen S, Andersen T, Gehrchen M.

Published in Journal of Orthopaedic Surgery. 2018 May 5;26(2).

III. Distraction-to-stall versus targeted distraction in Magnetically Controlled Growing Rods

Casper Dragsted, Sidsel Fruergaard, Mohit J Jain, Lorenzo Deveza, John Heydemann, Søren Ohrt-Nissen, Thomas Andersen, Martin Gehrchen, Benny Dahl, Texas Children's Hospital Spine Study Group

Submitted for publication in Journal of pediatric orthopaedics – Currently under review

IV. Does magnetically controlled growing rods lead to low bone mineral density in instrumented vertebrae? – a feasibility study.

Casper Dragsted, Søren Ohrt-Nissen, Thomas Andersen, Niklas Tøndevold, Benny Dahl, Martin Gehrchen

Submitted for publication in Spine, December 2019

Introduction

Definitions

Early-onset scoliosis (EOS) is defined as “scoliosis diagnosed before the age of ten, regardless of etiology”[1,2]. Scoliosis in general is defined as a curvature of >10° in the coronal plane. Adolescent idiopathic scoliosis (AIS) is the most common scoliosis in adolescents, whereas EOS is a more rare condition with unknown prevalence[3–5]. EOS covers a heterogeneous population of patients ranging from mild and resolving to severe and progressive deformity[6]. The underlying cause is either congenital or structural deformity, neuromuscular diseases or a syndrome associated with scoliosis[1,7]. If no underlying cause is identified, the etiology is termed idiopathic.

Background

EOS is potentially a severe condition. Because of the onset at a young age, EOS can lead to decreased pulmonary function and congenital/structural deformities can cause thoracic insufficiency syndrome[8–10] (Figure 1). Untreated EOS has been associated with increased mortality caused by pulmonary failure[11–13]. Pulmonary function is difficult to measure in children less than 5 years of age and in children with neuromuscular and some syndromic diseases[10]. Therefore, treatment is mainly guided by the size of the major curve. Other factors have been examined as surrogate measures of pulmonary function. One is assessing thoracic height which to some extend correlate with pulmonary function[14]. Dimeglio and Canavese have published commonly used normal values of thoracic and spinal growth during childhood and adolescence[15–18]. T1T12 thoracic height increases approximately 1.3 cm/year from birth to 5 years, 0.7 cm/year from 5 to 10 years of age and 1.1 cm/year during puberty[16]. Early fusion of

the thoracic spine before skeletal maturity can lead to decreased pulmonary function on a restrictive basis due to low thoracic height and a T1T12 height of less than 22 cm has been suggested to result in low forced vital capacity (FVC) [19–22]. These results underline the importance of ensuring growth of the thoracic spine as one of the goals in treating patients with EOS. In a large study of pulmonary function in idiopathic EOS and AIS, preoperative main thoracic coronal curve size correlated with pulmonary function, and overall, curve sizes >70° resulted in predicted FVC < 65%[23]. Moreover, patients with idiopathic EOS had larger preoperative curves resulting in even lower pulmonary function compared with AIS[23]. Beside the pulmonary perspective, the three-dimensional (3D) changes in larger scoliotic deformities might lead to altered sagittal shape and balance and thus influence functional outcomes and health-related quality of life[24]. This is evident from studying radiographic parameters in adult spinal deformity[25].

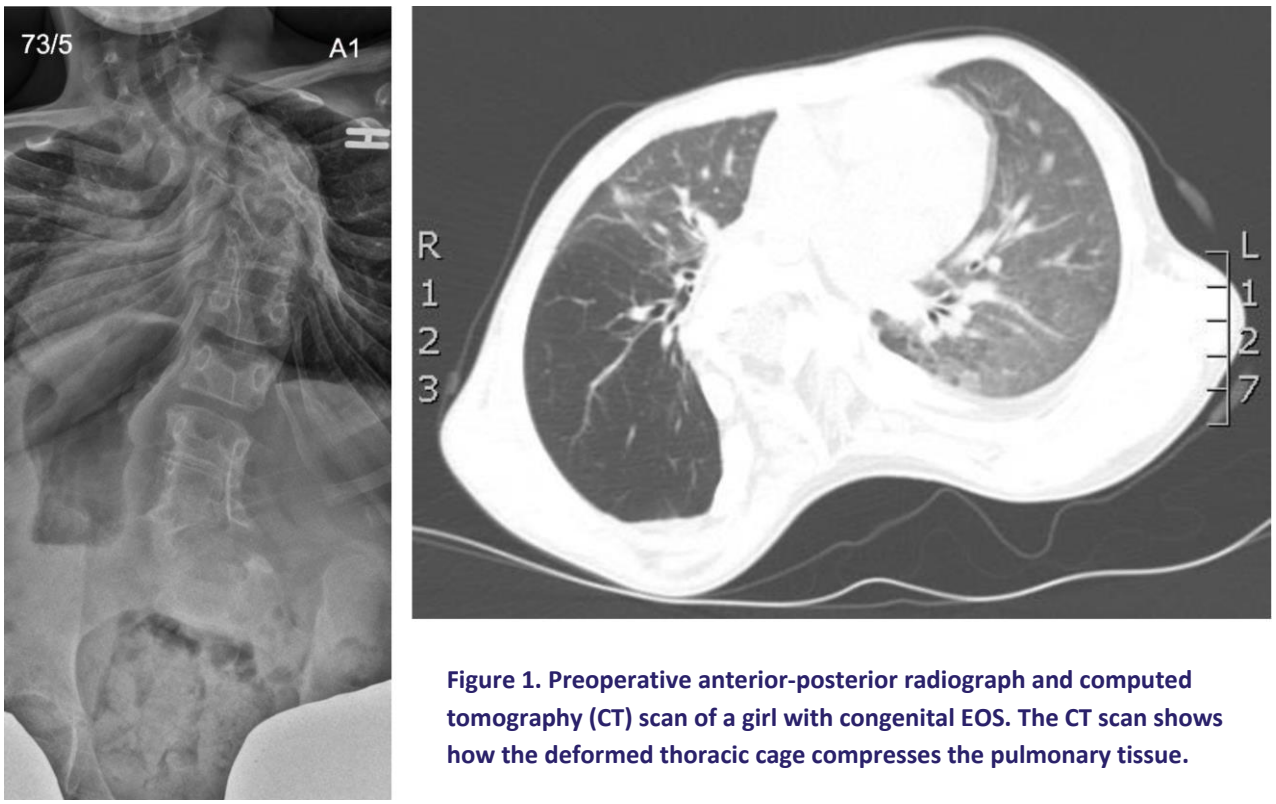


Figure 1. Preoperative anterior-posterior radiograph and computed tomography (CT) scan of a girl with congenital EOS. The CT scan shows how the deformed thoracic cage compresses the pulmonary tissue.

The natural history of EOS is difficult to assess as few patients are left untreated. Long term studies of AIS show that curves greater than 50° at the end of growth tend to progress over time[11,26,27]. The severity and age at onset strongly predicts progression of the scoliosis[28–30] underlining the impact of the deformity in EOS. Patients with EOS will have to live with the deformity throughout their entire life. Hence, the goal is not only ensuring growth to preserve pulmonary function, but also to halt progression of the deformity ensuring long-term cosmetically and functionally acceptable outcome.

Classification

The heterogeneity of EOS warrants the need for a classification system to support a uniform language for future research and to guide treatment for individual patients[31–34]. Recently, the Classification of Early-Onset Scoliosis (C-EOS) was developed including etiology, major curve angle (MCA) and kyphosis as the three main variables, and annual progression rate (APR) as an optional modifier[1] (Figure 2). Its content and cut-off values are to some extent based on expert consensus and require further validation. The reliability of the C-EOS has been assessed in a single study using an online survey including only written information and no measurements of radiographs[35]. Moreover, the APR was not assessed in that study. Classifying etiology of the patients depends on the provided information about the patient and is correctly assessed with kappa statistics. However, assessing reproducibility of the continuous variables MCA, kyphosis and APR requires other statistical analyses including errors of measurements[36,37]. Measurement errors have been reported for AIS[38–41], neuromuscular[42] and congenital scoliosis[43]. However, only one study focused entirely on non-congenital EOS reporting a measurement variability of 7.3° for major curve angle with pre-determined end-vertebrae[44]. In a clinical setting, end vertebrae are not pre-determined, and measurements are often repeated on the

same patient over time by different surgeons. Knowledge of these measurement errors are of great importance for making the right decisions for the individual patient.

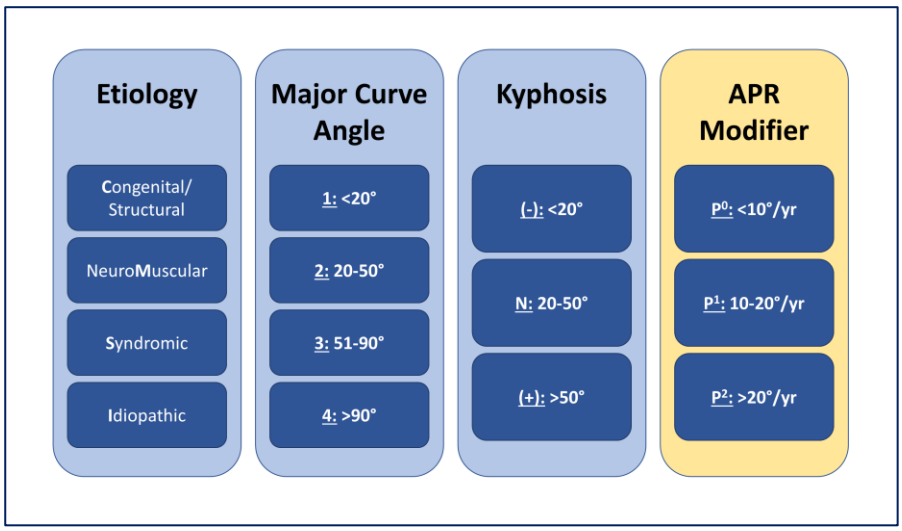


Figure 2. The Classification of Early-Onset Scoliosis (C-EOS)

Treatment strategy and surgical intervention

The treatment strategy varies according to the etiology, and generally, there is little consensus on the treatment principles, timing of intervention and implant choice[32,45–47]. Conservative treatment is the first choice for most patients. In children <5 years with idiopathic EOS, a derotational cast can reduce and occasionally cure the deformity[48,49], but more frequently a cast can delay the need for surgical intervention[50]. In older patients with EOS, a full-time brace is the preferred treatment[51]. The efficacy of bracing has been proved for AIS[52,53], but whether these results are transferrable to an EOS population is generally unknown. Studies of brace treatment in EOS are of low evidence and when to convert to surgical intervention is debatable[51]. Guidelines suggest surgical treatment in patients with curve progression despite bracing or severe curves >60° with substantial remaining growth potential[54].

Various growth-preserving surgical techniques have been suggested and these are classified as either distraction based, compression based or growth guided systems[55]. Harrington was the

first to introduce a distraction based non-fusion technique back in 1963[56]. The technique was later modified[57] and provided the basis for the development of a dual growing rod technique often referred to as traditional growing rods (TGR). TGR has been shown to effectively correct the deformity and results in increased spinal height[58]. However, it requires repetitive open surgical procedures for lengthening every 6 months with high complication and infection rates[58–61]. Therefore, a magnetically controlled growing rod (MCGR) was developed which allows non-invasive lengthening to be performed in an awake patient in the outpatient clinic[62–66]. Several case-series have shown that MCGR treatment effectively corrects the coronal deformity and results in spinal growth[63,65,74–80,66–73].

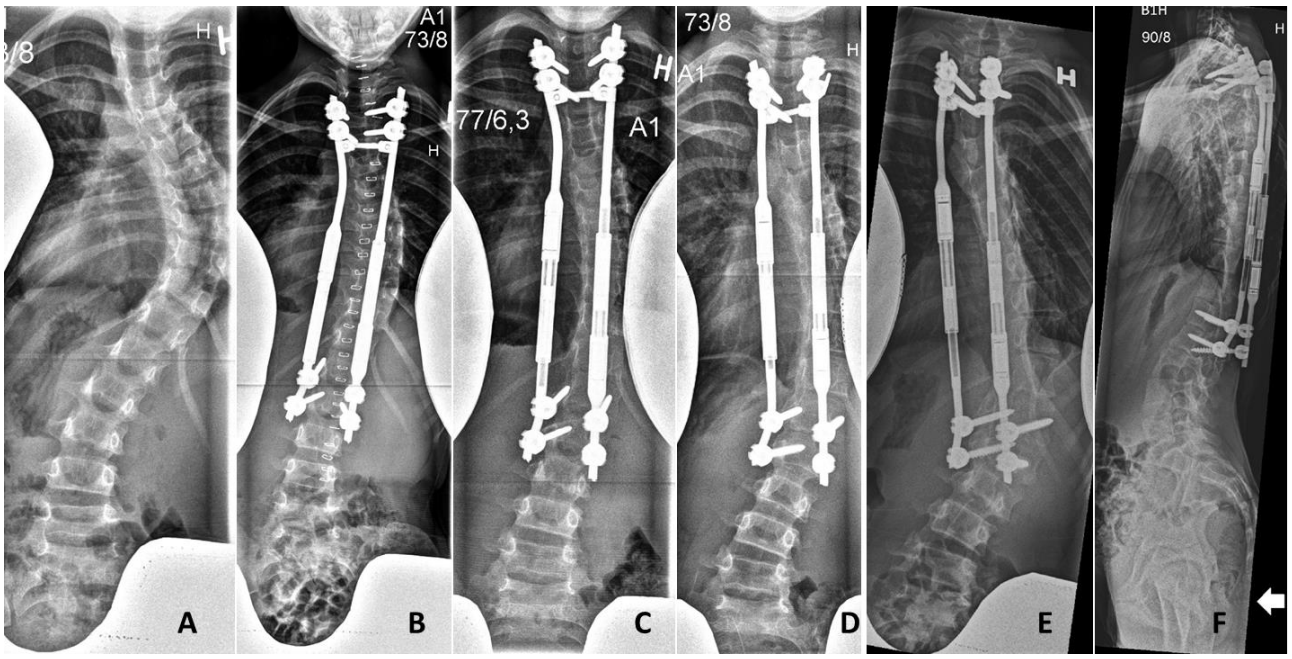


Figure 3. The first patient operated with magnetically controlled growing rods at our center. An 8-year-old girl with idiopathic EOS and a preoperative major curve angle of 77°. Radiographs shown are preoperative (A), postoperative (B), at 1.5-year (C), 3-year (D) and 4.5-year postoperatively, antero-posterior (E) and lateral (F). Postoperatively, major curve was reduced to 41°. After 1.5 years she developed pain at the distal anchor site. A CT-scan showed screw loosening and she was re-operated with exchange of both rods. She had undergone 27 distractions at latest radiographic follow-up and total achieved distraction was 53.2 mm on the concave rod and 36.5 on the convex rod. T1T12 and T1S1 increased from 199 mm and 326 mm preoperatively, to 235 mm and 366 mm at 4.5-year follow-up, respectively. She just had her menarche at the latest follow-up.

The lengthening is usually performed with the patient in a prone position. The MCGR actuator is located with a magnet and the external remote control (ERC) is applied to the skin causing the internal actuator to distract (Figure 4). The distractions are most often performed following either of two principles: a maximum force distraction ("distraction-to-stall") or a targeted distraction. In distraction-to-stall, the distraction is stopped when the internal actuator slips (the sensation is termed "clunking") or the patient reports discomfort. In targeted distraction, the lengthening mimics normal spinal growth following growth charts ("tail-gating principle") or at a fixed rate by programming the desired distraction on the ERC. Distractions are monitored with ultrasound[81,82], fluoroscopically[76] or with radiographs. In general, there is little consensus on the optimal rod placement and fixation, optimal distraction method, the time interval between lengthening and the desired distraction amount per lengthening[47,64,83]. This highlights the need for further studies.

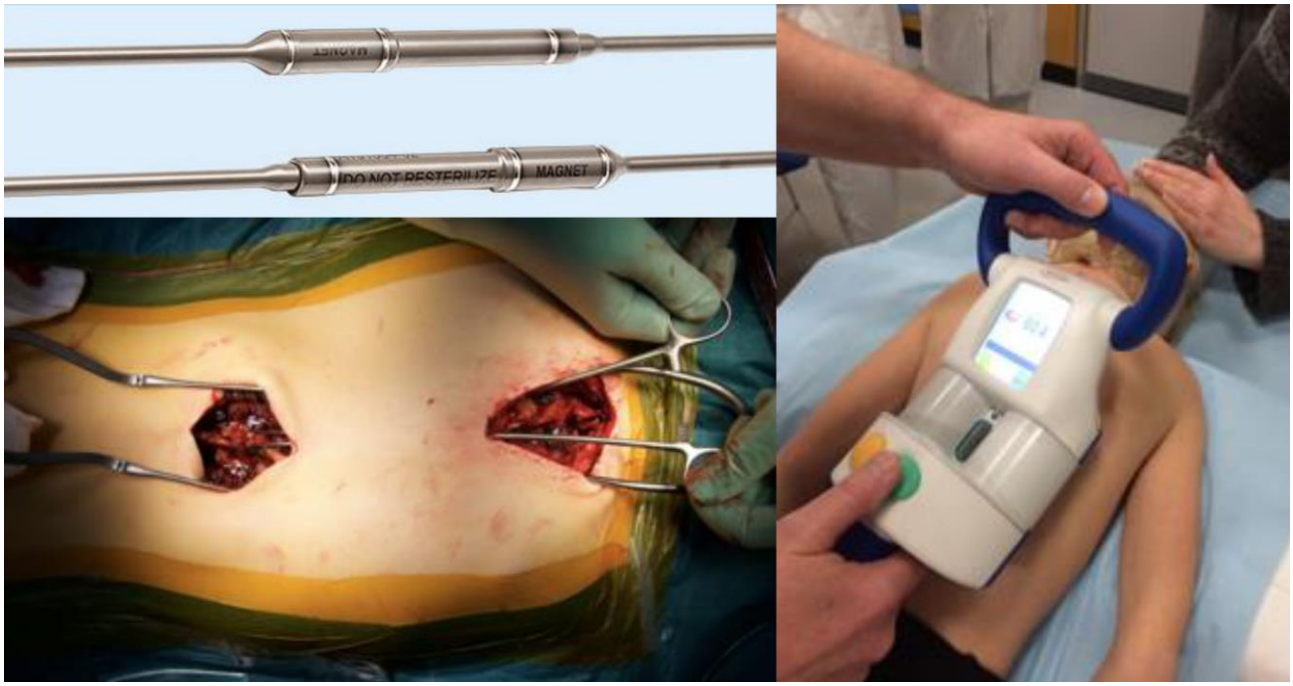


Figure 4. Upper left: Magnetically controlled growing rods. Lower left: The surgical procedure with subfascial insertion of the rods through a dual skin incision. Right: An example of a lengthening procedure with the patient lying in a prone position.

Complications and outcome

The introduction of MCGR treatment has reduced the number of invasive procedures and infection rate compared to TGR[59,84,85]. However, complications (44.5%) and unplanned reoperation rates (33%) for MCGR remain high[86]. Implant-related complications include screw or hook pull-out, rod breakage and rod distraction failure. The complication rate is higher for single-rod constructs and for patients converted from other growth instrumentations[70,71,86,87]. Moreover, rod breakage occurs presumably more often in 4.5 mm rods[86], but the young age of some patients require the use of small implants. Overall, the high complication rate in MCGR remains an unsolved problem.

Patients converted from other growth instrumentations have also been shown to achieve less spinal height with the MCGR treatment. For TGR, Sankar et al. showed that less spinal height is gained with every lengthening procedure, a phenomenon termed “the law of diminishing returns”[88]. It is thought to be caused by increased stiffness of the spine with every open procedure performed, which might also be the cause in MCGR conversion cases. However, whether this phenomenon applies to MCGR treatment in general is controversial[67,80,89–92]. Inherently, few results of patients graduating from MCGR have been published[80,89,93], and currently it is recommended to remove the MCGR at skeletal maturity and perform a definitive fusion of the spine[64,94]. Concerns have been raised about metallosis from debris around the actuator portion of the MCGR[95,96] which adds to the argument of removing the implant, but the long-lasting effect and consequences of this is unknown. No studies have assessed the consequences of MCGR on bone quality of the vertebrae within the instrumentation with bone mineral density (BMD). In other distraction-based techniques, a few studies have shown that the growth-instrumentation results in morphometric changes of the distracted vertebrae[97–99]. This

might be due to stress-shielding of the vertebrae within the instrumentation which theoretically would result in lower BMD. However, studies are required to confirm this hypothesis.

Objectives

The overall objective of this thesis was to assess the reproducibility of the C-EOS, examine the efficacy of MCGR treatment and its complications and compare different distraction principles. The following describes the objectives and hypotheses for each of the four studies:

I. Assess the agreement and reliability of the C-EOS and the accuracy of MCA, kyphosis and APR using standard error of measurement (SEM) and limits of agreement (LOA). We hypothesized that the C-EOS would show substantial agreement across all variables.

II. Assess curve correction and complications in patients treated with MCGR and report the efficacy of a distraction-to-stall lengthening procedure. Moreover, to compare outcome between idiopathic and non-idiopathic patients. We hypothesized that MCGR effectively corrected the deformity and distraction-to-stall resulted in a spinal height increase comparable to the literature.

III. Compare achieved distraction between a targeted distraction and a distraction-to-stall principle. Secondly, identify variables associated with achieved lengthening. We hypothesized that there was no difference between the two distraction principles.

IV. Investigate the feasibility of measuring BMD in the distracted vertebrae within the MCGR instrumentation. Secondly, compare this measure to BMD of the total hip and the vertebrae outside the instrumentation. We hypothesized that MCGR resulted in lower BMD of the vertebrae within the instrumentation.

Study designs

Early-onset scoliosis is a rare condition and only a minor proportion of the patients requires surgical intervention. Over a 5-year period, 27 patients have undergone MCGR treatment at our institution which underlines that randomized controlled studies in this population are not feasible, unless performed in a large multi-center setting. Moreover, with developments in implants and introduction of new, hypotheses might be outdated before a study is finalized. One solution is international multicenter databases; however, this limits the hypotheses to overall outcomes and details regarding lengthening procedures are typically not reported in these studies. Therefore, we designed study II and III as retrospective single center studies. Study IV is an explorative feasibility study with a cross-sectional design. The optimal design for testing the hypotheses in the study would have been a longitudinal design; however, this was not feasible within the time frame of this thesis and would expose each child to multiple radiation based DXA exams. This could not be justified before examining the feasibility in a cross-sectional design. For study I, we needed a consecutive and representative EOS cohort with no assessment of outcomes for which a retrospective study design was appropriate.

Subjects and materials

Figure 5 shows an overview of patients included in the four studies. For study I, we included a consecutive cohort of patients with EOS seen in our outpatient clinic from January 1, to June 30, 2015. We screened all patients under the age of 18 years at their visit with a diagnosis from one of the following ICD-10 diagnostic groups: DM40-DM43 (Deforming dorsopathies), DQ675 (Congenital deformity of spine), DQ76 (Congenital malformations of spine and bony thorax) or DQ87 (Other specified congenital malformation syndromes). Patients with previous spine surgery

were excluded resulting in 70 patients available for the study. The first 6 were enrolled for a training session and 4 were excluded due to insufficient full-length spine radiographs, leaving 60 patients for the final ratings.

In study II, we included and prospectively registered all patients treated with MCGR at our institution from November 2013 through August 2017. Patients with single-rod constructs or conversions from other growth instrumentations were excluded (2 patients). This resulted in 19 patients included in the study.

Study III included patients treated with MCGR at our institution and from one other tertiary referral center during the period November 2013, to January 2019. For this study, we only included patients with minimum 1-year follow-up and minimum 3 lengthening procedures. A total of 58 patients were treated with MCGR in the study period; 39 fulfilled the study criteria.

Study IV included a subgroup of patients treated with MCGR at our institution with the ability to stand/walk and with no structural deformities of the vertebrae of interest. Thirteen patients fulfilled the study criteria of which 11 underwent DXA scans.

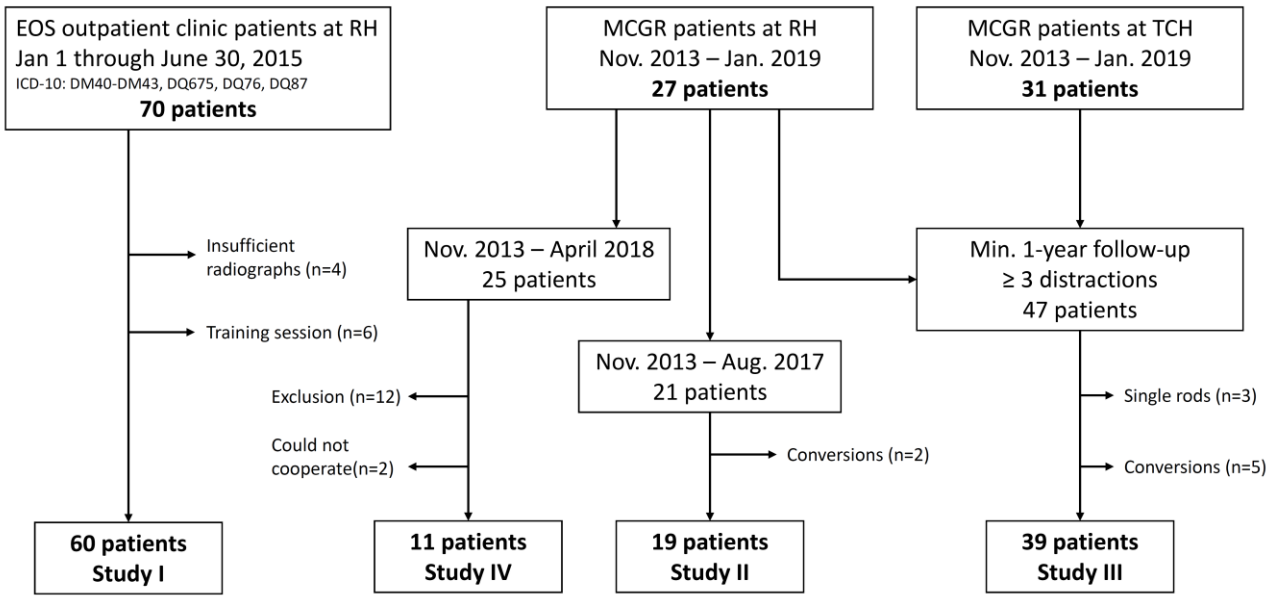


Figure 5. Flow-chart of included study populations. MCGR: Magnetically controlled growing rods, RH: Rigshospitalet, TCH Texas Children's Hospital

Methods

Study I was conducted according to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS)[100]. The study was conducted in a blinded test-retest setup including raters with different levels of experience in pediatric spine surgery. The primary author systematically summarized the patients' medical records in a case text provided to the raters together with two anterior-posterior radiographs taken minimum 6 months apart and one sagittal radiograph. The radiographs were unmarked with no pre-selected end vertebrae. The raters were asked to classify the etiology and measure MCA and global kyphosis. To avoid simple misclassification errors otherwise reported in the previous studies[1,35], we used the statistical software to calculate the APR and assign each measurement to the corresponding category in the C-EOS. The raters were given written instructions and a test-rating was performed on 6 patients to ensure all raters understood the task. Each case was rated twice by all raters with a minimum of two weeks between first and second rating.

For study II and III we included only primary MCGR treated patients. We excluded patients with single rod constructs and conversion cases as other studies already had suggested poorer outcome in terms of higher complication rates and less achieved lengthening[70,71,77]. Inherently, the population of EOS patients is very heterogenous, and by excluding patients with different outcomes we aimed to increase the validity of our results. In study II, achieved distraction, T1T12 and T1S1 increase were reported per year based on the measurement at latest follow-up and compared with the normative data reported by Dimeglio, Canavese et al[15–17]. In study III, achieved distraction was calculated as the mean within the first year after index surgery as some of the patients did not reach 2-year follow-up. Variables associated with achieved distraction were analyzed in a multivariable model.

In study IV, BMD was measured at different time points during treatment in patients with MCGR implants using areal BMD (aBMD) as the primary measure of interest. The measurements were performed according to guidelines from The International Society for Clinical Densitometry[101]. Areal BMD were measured in total hip area on both sides to represent a reference BMD of each patient, in the 3 vertebrae below the lower MCGR anchor point (zone b1-b3), at the anchor point (zone i0), and in the 3 vertebrae above the lower anchor point within the instrumentation (zone a1-a3) (Figure 6). We used the scanner software to exclude high density pixels from implant metal[102,103]. To account for differences in age and body habitus between the study participants, we calculated age-adjusted ($aBMD_{age}$) and height-for-age adjusted ($aBMD_{HAZ}$) Z-scores for aBMD using the LMS equation from a large reference population[104–106]. Moreover, we calculated a relative BMD of the instrumented vertebrae by dividing with total hip BMD.

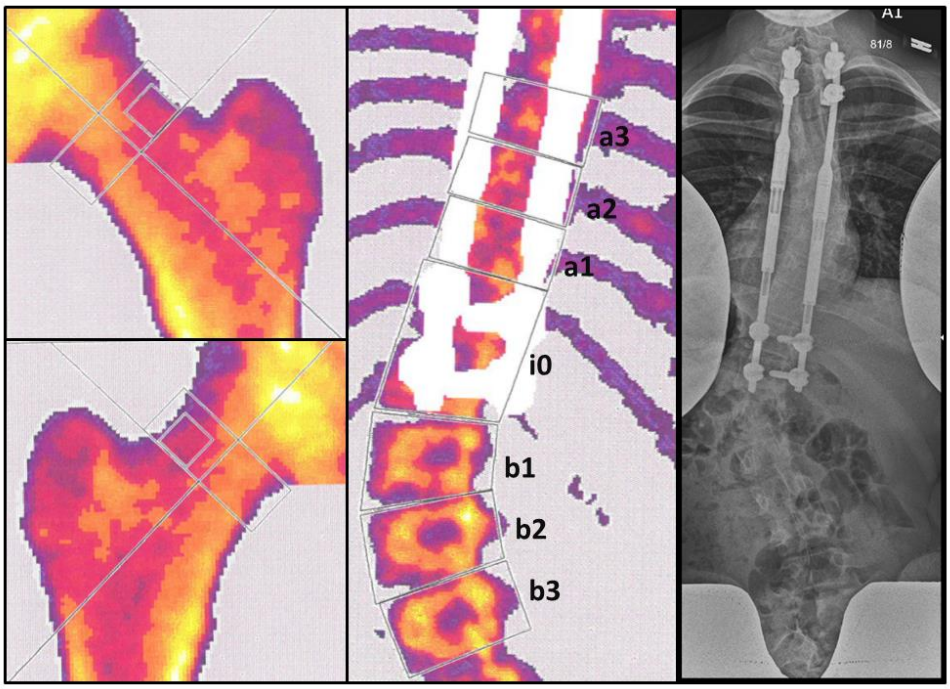


Figure 6. Areal bone mineral density (aBMD) measurements in a 14-year-old girl diagnosed with idiopathic EOS and treated with magnetically controlled growing rods. To the left: aBMD of left and right total hip; Middle: aBMD of the spine with the zones of interest: Vertebrae within the instrumentation (zone a1-3), at the lower anchor point (i0) and vertebrae below the instrumentation (zone b1-3); To the right: Anterior-posterior radiograph at the time om examination showing a major curve of 40 degrees.

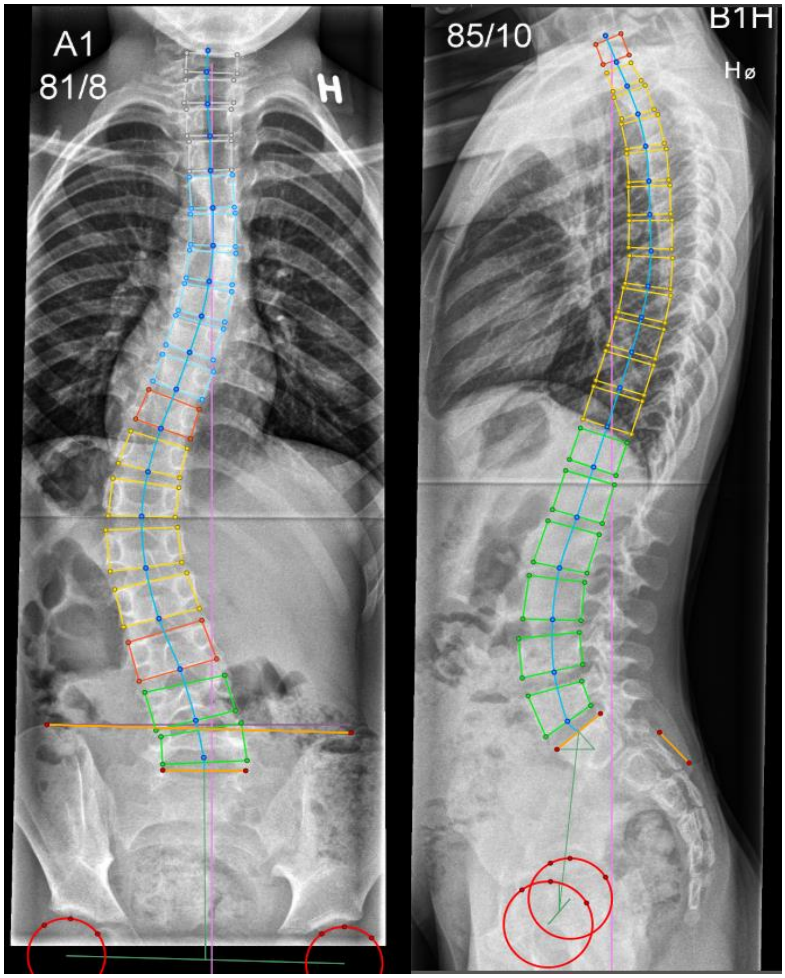


Figure 7. Example of angle measurements performed in the validated online imaging software KEOPS® (SMAIO, Lyon, France)

Radiographic measurements

To ensure high quality images, all radiographs were obtained in DICOM-format and uploaded to the validated online imaging software KEOPS® (SMAIO, Lyon, France)[107] (Figure 7). We measured MCA and global kyphosis angle according to the definitions in the C-EOS[1] and Scoliosis Research Society guidelines[108]. Measurement of thoracic height (T1T12), total spine height (T1S1) and achieved distraction was performed according to previously published studies on calibrated radiographs using the MCGR actuator width as reference[76,84,109] (Figure 8). In study II, achieved distraction was reported for each rod separately, whereas in study III it was reported as a mean of the two rods. All radiographic measurements were performed by the author of this thesis.

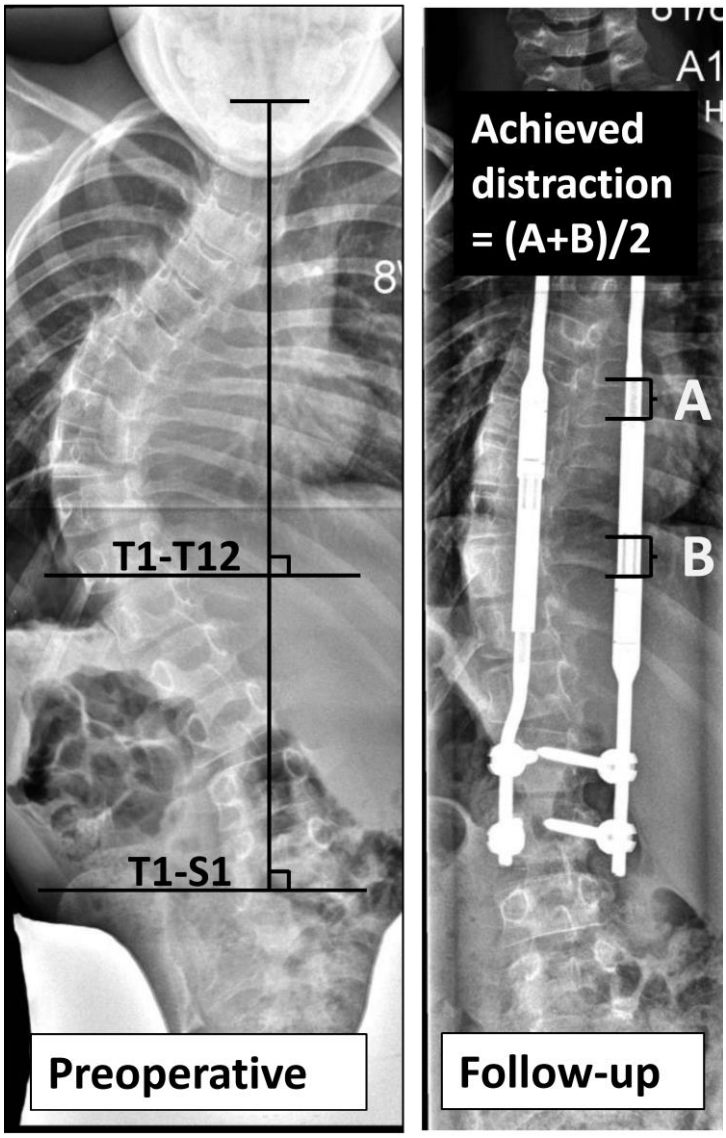


Figure 8. Examples of measurements of thoracic height (T1T12) and total spine height (T1S1) *(left)* and measurement of achieved distraction on the concave rod *(right)*.

Statistical considerations

Statistical analyses were performed in R (R Development Core Team, 2011, Vienna, Austria). A biostatistician was consulted when performing the statistical analyses. Data were generally visualized with histograms, quantile-quantile plots and scatter plots. A linear mixed effects model was used in study III to account for the correlation of repeated measurements and difference in length of follow-up between the groups. In the model comparing achieved distraction between the two groups we adjusted for the number of instrumented vertebrae.

In study I, overall agreement was reported with crude frequency of agreement between all raters.

Reliability of the classification was assessed with Fleiss' kappa (ƙ) and for the continuous variables (MCA, kyphosis and APR) with intraclass correlation coefficient (ICC)[36,37,110,111]. The linear mixed effects models in study I were constructed as variance component models from which the intra-rater and inter-rater standard error of measurements (SEM) were retrieved[112–114]. From SEM, we calculated limits of agreement (LOA) which describes the value by which there is a 95% probability of a true difference between two measurements on the same patient.

Approvals

The studies in this thesis were approved by the Danish Patient Safety Authorities (j.no: 3-3013-1911/1/), Data Protection Agency (j.no.: 2012-58-0004) and the Texas Children's Hospital institutional review board (j.no.: H43238). Study IV was approved by the regional committee on health research ethics (j.no.: H-18010812) and written informed consent was retrieved from both parents/legal guardians.

Summary of results

Paper I

Reproducibility of the Classification of Early-Onset Scoliosis (C-EOS)

Etiology of the included patients was congenital/structural (n =20), neuromuscular (n =13), syndromic (n =8) or idiopathic (n =19). We found substantial agreement for etiology (ƙ=0.80), almost perfect for MCA (ƙ =0.86), moderate for kyphosis (ƙ =0.52) and substantial for APR (ƙ =0.61) (Table 1). Disagreement in etiology was pronounced for syndromic patients and patients with neural axis abnormalities. There was no marked learning effect from first to second rating. Inter-rater LOA for MCA was 12.8°, for kyphosis 20.6° and for APR 17.4°. We found considerable variation in LOA between different etiologies, largest for neuromuscular patients and lowest for idiopathic patients. Limits of agreement for APR was larger than the 10°/year increments in the C-EOS regardless of etiology.

Table 1. Interrater reliability and agreement for the C-EOS for 1. and 2. rating and for both ratings combined.

	Agreement (%)	kappa (95% CI)	ICC (95% CI) *
Etiology			
Rating 1	73.3%	0.78 (0.69, 0.87)	-
Rating 2	78.3%	0.82 (0.73, 0.91)	-
Both ratings	75.8%	0.80 (0.73, 0.86)	-
MCA			
Rating 1	90.0%	0.91 (0.84, 0.98)	0.97 (0.95, 0.98)
Rating 2	78.3%	0.80 (0.70, 0.91)	0.98 (0.96, 0.98)
Both ratings	84.2%	0.86 (0.80, 0.92)	0.97 (0.96, 0.98)
Kyphosis			
Rating 1	55.0%	0.51 (0.35, 0.66)	0.85 (0.78, 0.90)
Rating 2	56.7%	0.53 (0.38, 0.67)	0.88 (0.83, 0.92)
Both ratings	55.8%	0.52 (0.41, 0.62)	0.87 (0.82, 0.89)
APR			
Rating 1	71.7%	0.57 (0.40, 0.74)	0.74 (0.64, 0.82)
Rating 2	81.7%	0.66 (0.49, 0.84)	0.81 (0.74, 0.87)
Both ratings	76.7%	0.61 (0.50, 0.73)	0.77 (0.71, 0.82)

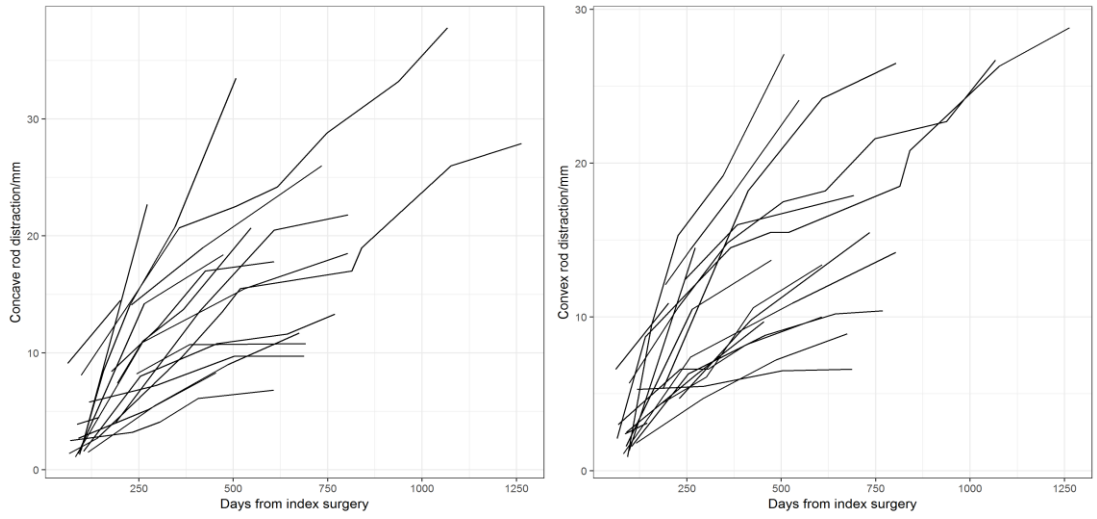
*Intraclass correlation coefficient

Paper II

Use of a distraction-to-stall lengthening procedure in Magnetically Controlled Growing Rods – a single-center cohort study

The study included 19 patients (8 idiopathic and 11 non-idiopathic) treated with MCGR. Mean age at surgery was 9.7±1.9 years with a median follow-up of 1.9 years (iqr: 1.3-2.2). MCA improved from median 76° (iqr: 64-83) preoperatively, to 42° (iqr: 32-51) postoperatively ($p<0.001$) corresponding to a curve correction of 43% (iqr: 33-51) and a median corrections index (CCI) of 108% (iqr: 91-117). The correction was maintained at 1 and 2-year follow-up. Median annual T1-T12 and T1-S1 height increase was 10mm (iqr: 6-16) and 11mm (iqr: 7-33), respectively. Median achieved distraction per year was 10.3mm (iqr: 6.4, 12.9) on the concave rod and 8.2mm (iqr: 6.8, 11.6) on the convex rod. A total of 159 distraction procedures were performed, 83.5% of these were distracted-to-stall and 16.5% were stopped due to discomfort. Five patients had implant-related complications (1 rod breakage, 3 screw pull-out and 1 iliac hook fixation failure) leading to unplanned reoperation in 4 patients. Finally, we found no difference in curve correction, spinal height increase, achieved distraction or complications between idiopathic and non-idiopathic patients ($p\geq0.109$).

Figure 9. Spaghetti plots of achieved distraction on both rods, the concave side (left) and the convex side (right) respectively. Each line represents distractions in a single patient plotted against days from index surgery.



Paper III

Distraction-to-stall versus targeted distraction in Magnetically Controlled Growing Rods

This study included 39 patients treated with dual MCGR at two tertiary institutions. In group 1 (21 patients), lengthening was performed with a distraction-to-stall principle, and in group 2 (18 patients), with a targeted distraction principle. Mean age at surgery was 9.5±2.0 years. Etiology was congenital/structural in 7, neuromuscular in 9, syndromic in 3 and idiopathic in 20 patients. The two groups did not differ regarding age, etiologies and preoperative characteristics including T1T12 and T1S1 ($p \geq 0.13$). The mean time interval between distractions was 18 days (95% CI 10-25) shorter in group 1. Implant-related complications occurred in 10/39 patients, 5 in each group. In the linear mixed effects model adjusting for number of instrumented levels, we found no difference in achieved distraction between the groups (Figure 10). Variables found to be associated with achieved distraction in the univariable analysis were preoperative MCA, T1T12 and T1S1, and instrumentation length. In the multi variable analysis, preoperative MCA was the only independent variable associated with achieved distraction (Table 2).

Table 2. Multivariate analysis of variables significantly associated with achieved lengthening within the first year after index surgery.

Variable	Estimate, mm/year [95% confidence interval]	p-value
Preoperative major curve, °	0.15 [0.03; 0.26]	**0.012**
Instrumentation length, n	1.04 [-0.03; 2.10]	0.056
Preoperative T1T12, cm	0.11 [-0.61; 0.83]	0.753
R^2 for the model was 0.361		

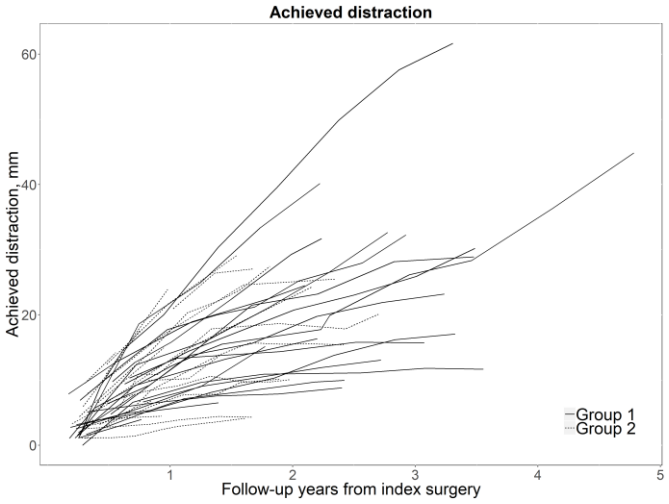


Figure 10. Spaghetti plot of achieved distraction in the two groups, distraction-to-stall (group 1) and targeted distraction (group 2). Each line represents distractions in a single patient.

Paper IV

Does magnetically controlled growing rods lead to low bone mineral density in instrumented vertebrae? – a feasibility study.

The study included DXA scans of total hip and spine in 11 patients treated with MCGR. Patients were scanned median 33 months from index surgery (range 5-57 months). We found statistically significant lower aBMD in vertebrae within the instrumentation (zone a) compared with total hip aBMD ($p = 0.002$), and lower aBMD compared with vertebrae below the instrumentation (zone b) but not statistically significant ($p = 0.063$) (Figure 6 and Figure 11). Areal BMD measurements in zone b were only available in 6 patients. Equal results were found by comparing $aBMD_{age}$ and $aBMD_{HAZ}$ Z-scores between vertebrae within the instrumentation, vertebrae below the instrumentation and total hip, respectively. We found no association between time from MCGR index surgery and relative aBMD or $aBMD_{HAZ}$ Z-score for vertebrae within the instrumentation (Figure 12).

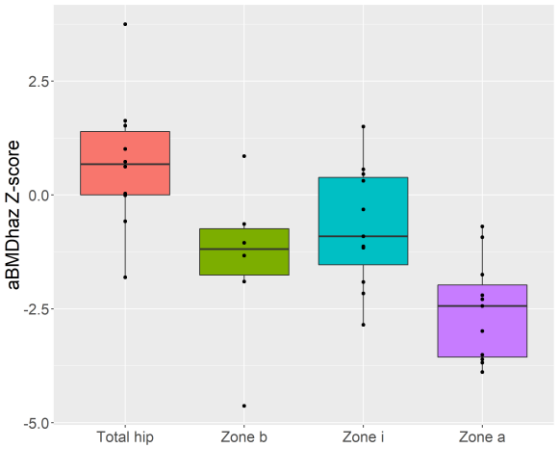


Figure 11. Boxplot of height-for-age adjusted areal bone mineral density ($aBMD_{HAZ}$) Z-score for total hip (mean between right and left), vertebrae below the instrumentation (Zone b), vertebra at lower anchor site (Zone i) and vertebrae within the instrumentation (Zone a). According to international guidelines a Z-score of <-2 is defined as low bone mineral density.

Figure 12. Relative areal bone mineral density (relative aBMD) plotted against time from index surgery. Relative aBMD was calculated as aBMD of instrumented vertebrae divided by total hip aBMD. Linear regression lines and corresponding p-value for the linear models are shown (blue).

Discussion

Classification – a guide to treatment?

The reproducibility of the C-EOS was examined in study I and reliability was overall comparable to the original study by Williams et al.[1] and the study by Cyr et al.[35]. However, in these studies specific measurements of MCA and kyphosis were provided to the raters in a text; hence, the results from these studies do not validly describe the reliability of the C-EOS. Moreover, reliability reported with kappa and ICC is difficult to interpret, whereas the accuracy of measurements as reported in study I with LOAs can easily be translated to clinical practice[36]. Limits of agreement for MCA was comparable to previous studies reporting measurement errors for individual etiologies[42–44] and somewhat larger than reported for AIS[40]. However, the existing studies of measurement errors vary in setup, statistics and the use of premarked radiographs which makes comparisons difficult[40]. The measurement errors reported in this thesis are representative of measurements performed in a clinical setting on a patient with EOS.

There was considerable variation in LOAs between different etiologies for all continuous variables in study I. This is not surprising considering the heterogeneity of this population, but nonetheless remarkable that LOA for neuromuscular patients is twice that of idiopathic patients. Regardless of etiology, the LOA for APR exceeded the 10°/year increments in the C-EOS. As APR is time-dependent, a time interval between radiographs less than one year results in multiplication of the measurement error. Therefore, APR is not meaningful in its current definition and should be based on more than two radiographs or a time-interval of minimum 1 year between radiographs.

We found substantial agreement for classifying etiology; however, in 24% of the cases, at least one rater disagreed with the others mainly regarding two specific issues. Firstly, patients with neural

axis abnormalities were classified as either idiopathic or neuromuscular. This issue is important considering the prevalence of neural axis abnormalities in presumed idiopathic EOS is 19%[115]. Secondly, disagreement was found among patients with syndromes characterized by neurological impairment and/or structural deformities, which is apparent in many syndromes associated with scoliosis[7]. Despite suggesting a ranking of etiologies in the original paper[1], there are inconsistencies in the text describing each etiology, and further specification might improve the reliability of the classification.

Only a few studies have assessed the content and cut-off values in the C-EOS[116,117]. Independently, etiology, MCA and kyphosis are associated with outcome after surgery[23,79,118,119], but how they combine to form certain risk profiles needs further investigation[117].

Overall, the C-EOS provides a reproducible common language for patients with EOS; however, the validity of the contents and its ability to guide treatment require continuous research using the classification.

Growth – what do we achieve with MCGR?

Study II and III reported outcomes of MCGR treatment using total spine height (T1S1), thoracic spine height (T1T12) and achieved distraction in accordance with previous studies. In study II we reported distraction on each rod separately and in study III a mean between both rods. Details regarding measurements of achieved distraction have been inconsistently reported in previous case-series[65–67,69,73,75,77,78]. Moreover, alterations in sagittal shape and progression of the deformity outside the instrumentation influence measurements of spinal height in the coronal plane. This is evident from study II where some patients had very limited increase in spinal height despite the MCGR being successfully distracted. To overcome this, sagittal and 3-dimensional

spine length measurements has recently been suggested as a way of measuring spine dimensions; however, no normative values exist and correlation to standard growth measures and pulmonary function is unknown[120,121]. Dimeglio and colleagues' data on normal spine growth is still the most well-established normative data, and achieved distraction in study II and III was comparable to the 1.1 cm/year of normal thoracic height gain during the growth spurt.

Nevertheless, it is evident from the linear plots in study II and III that some patients do not achieve substantial distraction during their lengthening procedures. This is in line with other case-series of MCGR treated patients reporting a wide range in achieved distraction[89,93]. The question is whether treatment with MCGR can be justified in these patients. However, first these patients need to be identified. We attempted to do so in the multivariable analysis in study III, but the model could only explain around one third of the variation in achieved distraction. One reason may be a lack of remaining skeletal growth assessment. We included only age and preoperative spinal height in the analyses but no objective assessment of remaining growth potential such as the Sanders maturity classification[122,123]. This classification among others assess growth potential in prepubertal children during the growth spurt as opposed to the widely reported Risser grading which is only applicable in the last third of the growth spurt[124]. However, the Sanders classification does not provide the amount of expected remaining growth and only applies to children from 9 years of age. Nevertheless, a limited remaining growth potential might explain some of the variation in achieved distraction found in our studies, and we encourage future studies to systematically include and report growth potential assessments to better predict which patients will profit from the treatment.

Lengthening procedures

Increased focus has been directed towards the lengthening procedures in MCGR treatment. Study II is the first study to describe the use of a distraction-to-stall principle. In this study, achieved distraction and spinal growth were found to be satisfactory and comparable to the background population. Curve correction and complication rate were also comparable to previously published studies[65,71,74,75,85]. In the distraction-to-stall principle presented in this thesis, achieved distraction is only evaluated on radiographs taken every 6 months. This contrasts with the tail-gating principle where achieved distraction is closely monitored at each lengthening procedure[76]. Studies show that achieved distraction is less than expected from the amount entered the ERC[67,69,74,90], and this discrepancy seems to increase with the number of lengthenings[90]. Hence, if using a targeted distraction principle with a fixed rate of distraction, it is difficult to estimate the amount that needs to be entered the ERC for achieving the desired distraction. In study III, we aimed to compare this targeted distraction principle with the distraction-to-stall principle. We found no difference in achieved distraction using a linear mixed effects model in which we adjusted for number of instrumented levels and difference in follow-up between individual patients. Unfortunately, ERC measurements and occurrence of clunking was not consistently reported in both groups and thus could not be assessed. However, clunking does sometimes occur in the targeted distraction group, and if the programmed distraction is large enough, the two principles are probably equivalent.

In study II, distraction was stopped before “clunking” in 16.5% of the lengthening procedures due to the patient reporting discomfort. A concern with this method is that maximal “tensioning” could cause increased pain[73,93]. In the early phases of the MCGR treatment at our institution, two distractions were performed in short general anesthesia. Moreover, one distraction caused

pain in a patient where it was decided to reduce distraction in an additional procedure. All patients continued regular distractions afterwards without complications, and though not a scope of this thesis, we generally do not experience pain during lengthening procedures as a major problem. However, the one patient experiencing pain after distraction underlines that the treating surgeon must not blindly trust the occurrence of clunking before stopping distraction.

The time interval between distractions is the main focus in a planned multicenter randomized clinical trial[47]. In study III, the mean time interval between distractions was 18 days longer in the targeted distraction group; however, as previously described there was no difference in achieved distraction between the groups. Similarly, we found no association between the time interval and achieved distraction across all patients. Reading through the patient files, it was evident that many other factors determined this time interval such as travel distance to the hospital, coordination with other appointments, holidays and individual approaches. Some patients report discomfort in the period up to a lengthening procedure and an approach to this problem is sometimes a shortening of the interval between lengthening. There is probably not one ideal time interval for all patients. The distraction-to-stall principle theoretically accounts for these differences in time interval and it is simple and easy to implement.

Complications – can we avoid them?

Studies have reported MCGR to be safe and effective in correcting the deformity in EOS patients[63,65,66,75]. In accordance with the literature, we showed that MCGR effectively corrected the coronal deformity and that the correction was maintained throughout the lengthening procedures. A recent systematic review reported a 44.5% complication rate and a 33% unplanned revision rate with MCGR[86] which questions the word “safe” to describe the

treatment. However, the complication rate needs to be put in context with the 58% complication rate reported for TGR[59]. It is likely that modifications made to the early versions of the MCGR implant and experience with the treatment might have lowered the complication rate, though still a major unsolved issue in this treatment.

A large proportion of spinal height increase is achieved at index surgery[109], and studies show that additional curve correction with final fusion surgery is limited[80,125]. This supports the surgical strategy described in study II in intending maximal curve correction and distraction at index surgery. Concerns have been raised that this strategy stresses the rods and could lead to implant failure[47,83], but there is no evidence to support this hypothesis. Nevertheless, exactly how much intraoperative distraction applied is decided by the surgeon and probably adjusted to the strength of the anchor points.

In study II and III we found a reduction in the global kyphosis postoperatively, however, this reduction was not maintained during follow-up. This corresponds to other studies of both TGR and MCGR[63,70,74,78,119,126]. Due to the relatively large actuator portion of the MCGR, contouring of the rod to the kyphosis is challenging. This might explain the high rate of proximal junctional kyphosis reported for MCGR[66,78] which put stress to the proximal anchor and might lead to fixation failure. Various strategies to prevent PJK have been proposed including a hybrid hook/screw construct, but the solution is not straightforward and requires future studies to address this problem[64,83,119,126].

Consequences of growing rods

Studies of MCGR have mainly focused on curve correction, lengthening and complications, and few studies have assessed the consequences of growth instrumentation on the instrumented

vertebrae. In study IV we found lower bone quality in the vertebrae within the instrumentation measured with BMD compared with total hip BMD and with height-for-age matched normative data for lumbar vertebrae. The BMD of vertebrae within the instrumentation was lower than for vertebrae below the instrumentation, but not statistically significant. The cross-sectional design and the limited number of patients with measurements of BMD in vertebrae below the instrumentation make it difficult to draw any firm conclusions. In theory, the MCGR implant and continuous distractions would lead to stress-shielding of the instrumented vertebrae causing lower BMD[97,127] and the study supports this hypothesis. Other studies have described how distractive forces in TGR cause morphometric changes of the vertebrae within the instrumentation which could explain the lower aBMD found in study IV[98,99]. In adult spinal deformity, low BMD is associated with increased complication rates[128,129]. As bone mineral content gained through childhood and adolescence strongly determines the peak BMD, a low BMD of the spine might affect outcome after final fusion or later in adulthood. But whether a low BMD is inherent to the scoliotic spine or a result of MCGR treatment needs further examination.

Conclusions

In a representative and consecutive cohort, we found C-EOS reproducible with substantial agreement for etiology and excellent reliability for MCA. However; reliability was lower for kyphosis and APR, and we found disagreement for classifying syndromic patients and patients with neural axis abnormalities. The measurement errors of MCA, kyphosis and APR varied substantially according to etiology. Regardless of etiology, LOA for APR was larger than the 10°/year increments in the C-EOS, which questions the reproducibility of this variable in its current definition.

Overall, MCGR effectively corrected the major curve and correction was maintained throughout the lengthening procedures. The use of a distraction-to-stall principle resulted in satisfactory achieved distraction and spinal height increase with a complication rate comparable to previous studies. We found no difference in outcomes between a distraction-to-stall and a targeted distraction principle. The only variable independently associated with increased distraction was preoperative MCA.

Finally, we found evidence suggesting that MCGR results in lower aBMD of vertebrae within the instrumentation, but these findings need to be verified in a longitudinal setup.

Perspectives

The MCGR technique has been described as a game-changer in the surgical treatment of EOS. However, this is slightly overstated as many other growth-instrumentation implants have been available during the last decades. The high up-front costs with MCGR implantation results in cost savings only after 3-4 years of treatment compared with TGR[130,131]. Moreover, studies so far have not been able to show marked differences in health-related quality of life[132–134]. Long-term studies are required to prove the efficiency of MCGR over TGR and other growth instrumentations.

Removing the rods as a final treatment leaving a non-fused spine is not a viable option[94]. Studies suggest that TGR might be sufficient in achieving spinal fusion at skeletal maturity without the need for additional surgery[125,135]. However, concerns regarding metallosis[95,136] and long-term duration of the MCGR implant make implant removal and final fusion surgery the recommended treatment at this point[64]. Moreover, achieving a balanced spine in the sagittal plane by correcting the hypokyphosis induced by the MCGR is another argument for performing a

final fusion. These patients will have to live with their fused spine for the rest of their lives. In AIS, increased attention has been raised to non-fusion techniques such as vertebral body tethering[137,138]. Whether this technique could replace MCGR in the treatment of some the older MCGR candidates with flexible curves and preserve motion has yet to be examined. The challenge is that a newly developed technique shows promising results at short-term and end up replacing an existing treatment without providing better long-term results. We have only just begun to understand the long-term outcome of the Harrington instrumentation which underlines this problem. With MCGR, we still do not know whether we preserve growth or stimulate growth by applying distractive forces to the spine and what the consequences are of permanent changes in bone morphology and BMD. Nevertheless, the MCGR's ability to increase spinal height and correct the deformity raise the question as to whether we have solved the severe pulmonary problems associated with EOS.

The high complication and reoperation rates remain an unsolved problem. Implant-related complications are with the existing evidence not associated with specific distraction principles. Future studies will have to look in to proximal anchor fixation and PJK which is one of the major implant-related issues with this procedure[86,139]. The right patient selection seems to be the most important factor for a successful outcome, and this require a uniform language such as the C-EOS to describe the patients. Overall, the MCGR technique is a successful treatment for most patients and its non-invasiveness might extend its indications in the future as we gain more knowledge about this treatment and hopefully are able to reduce the complication rates for these already exposed patients.

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Paper I

Reproducibility of the Classification of Early-Onset Scoliosis (C-EOS)

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Abstract

Study design: Reproducibility study

Objectives: Assess the agreement and reliability of the classification of early-onset scoliosis (C-EOS).

Summary of background data: C-EOS is a promising tool for patients with early-onset scoliosis (EOS). However, the reliability has only been examined without measuring radiographs and not including the annual progression rate (APR) modifier.

Methods: We included a single-center consecutive cohort of patients diagnosed with EOS seen in our outpatient clinic. Patients had no previous spine surgery. Four raters rated 60 cases. Two anterior-posterior full spine radiographs, taken minimum 6 months apart, and one sagittal radiograph were measured twice by all raters in a blinded test-retest setup. Results were assessed using crude frequency of overall agreement (OA), intra- and interrater Fleiss kappa (κ) statistics and intraclass correlation coefficient (ICC). We calculated the 95% limits of agreement (LOA) for major curve angle (MCA), kyphosis and APR using a linear mixed effects model. Inter- and intra-rater LOA were analyzed for each etiology separately.

Results: Mean age was 8.7±3.4 years and the etiology were congenital/structural (n=20), idiopathic (n=19), neuromuscular (n=13) or syndromic (n=8). For etiology, OA was 75.8% and κ = 0.80. For major curve angle, OA was 84.2%, κ=0.86, ICC=0.97 and LOA=12.8°. For kyphosis, OA was 55.8%, κ=0.52, ICC=0.87 and LOA= 20.6°. For APR, OA was 76.7%, κ=0.61, ICC=0.77 and LOA=17.4°/year. Inter- and intra-rater LOA were generally largest for neuromuscular and smallest for idiopathic patients.

Conclusions: We found substantial agreement for etiology, however, with disagreement in certain cases. The reliability of MCA was excellent; however, somewhat lower for kyphosis and APR with less accuracy. The measurement errors of MCA, kyphosis and APR depended largely on the etiology. Regarding APR, LOA exceeded the 10°/year increments proposed in the C-EOS, suggesting a revision of this optional modifier.

Level of evidence: Diagnostic study level 1

Key points

- In the classification of early-onset scoliosis (C-EOS), agreement of etiology is substantial, almost perfect for major curve angle (MCA) and moderate for kyphosis.
- A clarification of etiology could improve agreement, and classification according to treatment strategy could improve the clinical use.
- We suggest that the annual progression rate (APR) is based on more than two radiographs or that the time interval between them is a minimum of 1 year.
- Measurement errors were considerable and generally largest for neuromuscular and smallest for idiopathic patients.

Introduction

The classification of early-onset scoliosis (C-EOS) is a newly developed and promising tool for patients with Early-Onset Scoliosis (EOS) [1] (Figure 1). Nevertheless, it is not yet widely used in the literature on EOS. A classification system generally serves three purposes: to guide treatment, to provide information about outcome and prognosis, and to form a common language for comparison of individual patients and scientific literature [2]. Reliable and widely accepted classification systems have been developed for adult spinal deformity (ASD) and adolescent idiopathic scoliosis (AIS) [3–5]. C-EOS is the first classification system for EOS, systematically developed by experts within the field and generally accepted in the research societies. However, the variables and cut-off points are, to some extent, based on expert opinion [1] and require additional studies to validate the content. Whereas the validity of the classification system is difficult to measure, the reliability and accuracy can more easily be studied [2,6]. To date, only one study by Cyr et al. has evaluated the reliability of the C-EOS [7]. The study was an online survey among members of the Children's Spine Study Group and the Growing Spine Study Group showing good to excellent reliability for the variables: etiology, major curve angle (MCA) and kyphosis. However, the annual progression rate (APR) was not included and measurements of major curve angle and kyphosis was provided in the text describing each case and not measured by the individual rater [7]. Moreover, the expected measurement error for MCA and kyphosis has not been sufficiently established in an EOS-only population. The measurement error must be considered in repeated measurements on the same individual [8] and is essential to account for in clinical decision making. Therefore, we conducted a reliability and agreement study of the C-EOS including the APR with raters of different experience measuring unmarked radiographs. The purpose was to assess the agreement and reliability of the C-EOS and the accuracy of continuous variables using standard error of measurement (SEM) and limits of agreement (LOA).

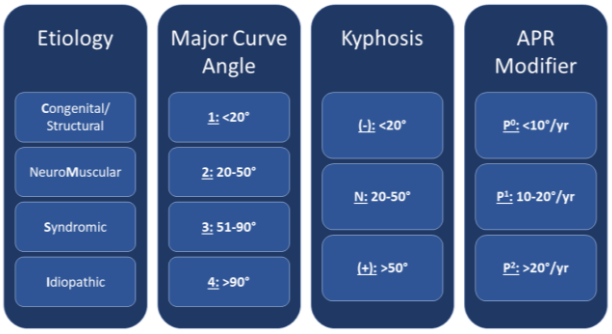

Figure 1. The classification of early-onset scoliosis (C-EOS).

Materials and methods

This study was performed according to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) [9]. A representative and consecutive cohort of patients were identified based on ICD-10 diagnoses. As all hospital visits at our institution are recorded with an ICD-10 diagnose, we were able to screen all patients seen in the outpatient clinic at our tertiary spine center under the age of 18 with a primary or secondary diagnosis from one of the following ICD-10 diagnostic groups: DM40-DM43 (Deforming dorsopathies), DQ675 (Congenital deformity of spine), DQ76 (Congenital malformations of spine and bony thorax) or DQ87 (Other specified congenital malformation syndromes). Patients diagnosed with scoliosis before the age of 10 and seen in the outpatient clinic from January 1 to June 30, 2015 were included. Exclusion criteria were previous spine surgery or insufficient radiographs (radiographs where C7 or the sacral endplate were not visualized). We identified 70 patients; the first 6 were enrolled for training purposes and 4 were excluded due to insufficient full-spine radiographs, leaving 60 patients for final analysis/assessment. None of the raters were

involved in the screening process. The primary author systematically summarized each patient´s medical history in a case text including age, sex, primary diagnosis, comorbidities, surgical history, neurological examination and Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) findings (Appendix 1). The primary diagnosis was retrieved from a chart review of the patient. The primary author did not assign a diagnosis in any of the cases and the names of the C-EOS etiologies (congenital/structural, neuromuscular, syndromic and idiopathic) were not used. The text was uploaded to the validated online image management software KEOPS® (SMAIO, Lyon, France) [10] together with two anterior-posterior (AP) full spine radiographs taken minimum 6 months apart and one sagittal radiograph (Figure 2). All radiographs were anonymized and uploaded in DICOM format to ensure high quality images. Radiographs were unmarked with no pre-selected end vertebra or endplates. Raters were given written instructions. For training purposes, the raters were asked to perform ratings of the 6 training cases and met to discuss the classification of these 6 cases to ensure they understood the written instructions. No agreement calculations were performed based on the training session. The subsequent ratings were performed individually with a minimum of 14 days between first and second rating, and cases were presented in a random order at each rating. Four raters were chosen to represent a broad range of experience levels: rater 1 and 2 (residents and research fellows), rater 3 (staff specialist) and rater 4 (senior staff specialist). All were familiar with the original study by Williams et al. [1] and the image management software used in this study. Raters were asked to classify the etiology and measure MCA and kyphosis. Based on these measurements, calculation of APR and categorization of MCA, kyphosis and APR were performed in the statistical software. The study was approved by the national health authorities (j.no.: 3-3013-1911/1) and data protection agency (j.no.: 2012-58-0004).

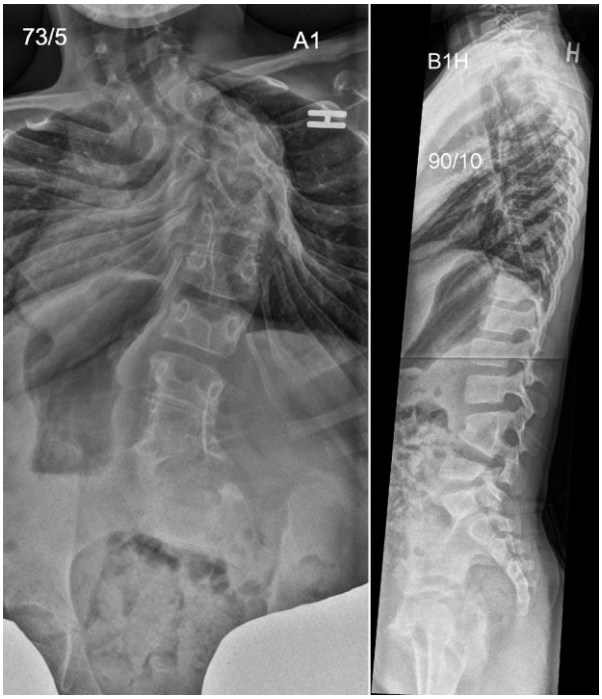

Figure 2. Examples of two patients in the study. To the left, an 8-year-old girl with multiple vertebral anomalies showing how poorly defined endplates can challenge the measurement of major curve angle. To the right, a 7-year old girl with thoracic butterfly vertebra and L3-L4 block vertebra; this case shows how the overall kyphosis can change depending on the chosen upper and lower levels of measurement.

Statistics

Statistical analyses were performed in R, version 3.5.2 (R Development Core Team, 2011, Vienna, Austria). Distributions were assessed with histograms and data presented as proportions (%), means with standard deviations (sd) or medians with inter quartile range (iqr). The software package “irr”, version 0.84, was used for assessing reproducibility. Overall agreement was assessed with crude frequency agreement (%). Fleiss kappa coefficients (κ) were used to describe inter- and intra-rater reliability of classification for all raters [11,12] and graded according to Landis and Koch as slight (≤0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) or almost perfect agreement (≥0.81) [13]. Inter-rater reliability between any 2 raters

Table 1. Inter-rater reliability and agreement for the Classification of Early-Onset Scoliosis (C-EOS) for each rating and both ratings combined.

	Crude frequency agreement (all raters)	kappa (95% CI)	ICC (95% CI)*
Etiology			
Rating 1	73.3%	0.78 (0.69, 0.87)	-
Rating 2	78.3%	0.82 (0.73, 0.91)	-
Both ratings	75.8%	0.80 (0.73, 0.86)	-
Major curve angle			
Rating 1	90.0%	0.91 (0.84, 0.98)	0.97 (0.95, 0.98)
Rating 2	78.3%	0.80 (0.70, 0.91)	0.98 (0.96, 0.98)
Both ratings	84.2%	0.86 (0.80, 0.92)	0.97 (0.96, 0.98)
Kyphosis			
Rating 1	55.0%	0.51 (0.35, 0.66)	0.85 (0.78, 0.90)
Rating 2	56.7%	0.53 (0.38, 0.67)	0.88 (0.83, 0.92)
Both ratings	55.8%	0.52 (0.41, 0.62)	0.87 (0.82, 0.89)
Annual progression rate (APR)			
Rating 1	71.7%	0.57 (0.40, 0.74)	0.74 (0.64, 0.82)
Rating 2	81.7%	0.66 (0.49, 0.84)	0.81 (0.74, 0.87)
Both ratings	76.7%	0.61 (0.50, 0.73)	0.77 (0.71, 0.82)

*Intraclass correlation coefficient

were assessed with Cohen's kappa [11]. For continuous variables (MCA, kyphosis and APR), reliability was described with intraclass correlation coefficients (ICC). A two-way random effects model, single measure, absolute agreement (ICC A,1) was used for inter-rater reliability and two-way mixed effects, single measure, absolute agreement (ICC A,1) for intra-rater reliability [11,12]. ICCs were graded as poor (≤0.50), moderate (0.50-0.75), good (0.76-0.90) or excellent (≥0.90) [14,15]. The accuracy of measurements was assessed with a linear mixed-effects model using the software package "lme4"; from which inter- and intra-rater SEM were calculated. Inter-rater SEM = √(rater variance + within-subject variance) and intra-rater SEM = √(within-subject variance). The 95% LOA, also referred to as the variability of measurements in some papers, was calculated as LOA = 1.96 x √2 x SEM [6,16,17]. Measurements were visualized with residual plots and modified Bland-Altman plots according to Jones et al. [8,16]. A biostatistician aided in performing the statistical analyses.

Results

The mean age of the patient cases was 8.7±3.4 and etiology, based on the majority of ratings for each case, was congenital/structural (n =20), neuromuscular (n =13), syndromic (n =8) and idiopathic (n =19). Median MCA was 40° (IQR: 29-60, range: 10-129), median kyphosis was 42° (IQR: 33-52, range: 12-124) and median APR 1.4° (IQR: -2.6-7.9, range -16.4-65.7). The mean time interval between first and second AP radiograph was 355 days (range: 188-782).

Inter-rater kappa coefficients for both ratings showed substantial agreement for etiology (0.80), almost perfect for MCA (0.86), moderate for kyphosis (0.52) and substantial for APR (0.61) (Table 1). Similarly, inter-rater ICCs were excellent for MCA (0.97) and good for kyphosis (0.87) and APR (0.77). Comparable patterns were seen for intra-rater agreement and reliability with

Table 2. Intra-rater agreement and reliability for the Classification of Early-Onset Scoliosis (C-EOS) for each rater.

	Crude frequency agreement	kappa (95% CI)	ICC* (95% CI)
Etiology			
Rater 1	95.0%	0.93 (0.85, 1)	
Rater 2	90.0%	0.86 (0.75, 0.97)	
Rater 3	88.3%	0.83 (0.71, 0.95)	
Rater 4	98.3%	0.98 (0.93, 1)	
Major curve angle			
Rater 1	95.0%	0.92 (0.82, 1)	0.99 (0.98, 0.99)
Rater 2	96.7%	0.97 (0.87, 1)	0.98 (0.97, 0.99)
Rater 3	88.3%	0.80 (0.66, 0.95)	0.97 (0.96, 0.99)
Rater 4	90.0%	0.83 (0.71, 0.97)	0.98 (0.95, 0.98)
Kyphosis			
Rater 1	86.7%	0.71 (0.53, 0.90)	0.97 (0.94, 0.98)
Rater 2	85.0%	0.65 (0.42, 0.89)	0.90 (0.93, 0.94)
Rater 3	78.3%	0.51 (0.28, 0.75)	0.89 (0.81, 0.94)
Rater 4	75.0%	0.57 (0.37, 0.76)	0.87 (0.79, 0.92)
APR			
Rater 1	86.7%	0.62 (0.38, 0.86)	0.84 (0.75, 0.90)
Rater 2	88.3%	0.65 (0.42, 0.89)	0.86 (0.78, 0.91)
Rater 3	88.3%	0.65 (0.42, 0.89)	0.81 (0.71, 0.88)
Rater 4	85.0%	0.58 (0.34, 0.83)	0.83 (0.74, 0.90)

*Intraclass correlation coefficient

no marked differences between raters (Table 2). Comparing ICC and kappa values between ratings showed no marked learning effect from rating 1 to 2 (Table 1). Inter-rater SEM for MCA was 4.6° and the corresponding LOA was 12.8°. For kyphosis, inter-rater SEM was 7.4° and the corresponding LOA 20.6°. For APR, inter-rater SEM was 6.3° and the corresponding LOA was 17.4° (Table 3). Intra-rater SEM was similarly lowest for MCA and highest for kyphosis (Table 3). Finally, we found a marked difference in measurement errors between different etiologies (Table 3). The individual measurements of MCA and kyphosis and the corresponding LOAs are shown in modified Bland-Altman plots (Figure 3a and 3b).

Discussion

In this reproducibility study of the C-EOS we included a consecutive and representative cohort of 60 patients. Four raters with different levels of experience measured all radiographs and assessed etiology in a blinded test retest setting. Agreement of etiology was substantial. The reliability of MCA was excellent, although somewhat lower for kyphosis and APR. The measurement errors of MCA, kyphosis and APR varied according to etiology.

Agreement and reliability are terms often used interchangeably to describe the reproducibility of a classification system or a measurement [6,11,12]. Kappa statistics are used to describe reliability of nominal and ordinal variables [9,11,18]. We have presented kappa coefficients for all variables in the C-EOS for comparison with

the study by Cyr et al. [7], knowing that the numbers might differ due to a different study setup and sampled population. In their study, the authors used a random sampling of patients with equal distribution of etiologies which reduces the "by chance agreement" and increases the kappa value [18]. In contrast, we included a consecutive population of patients with unequal distribution of etiology which from our perspective better represents a clinical setting.

Reliability of the continuous variables MCA, kyphosis and APR are more appropriately assessed with ICC. Not surprisingly, reliability assessed with ICC was good to excellent for continuous variables as ICC is a ratio depending on the variation between study subjects [6,12]. The variation of MCA and kyphosis in a population of EOS patients is expectably large, ranging from mild scoliosis not requiring treatment to severe progressive deformities [19]. Consequently, the accuracy of measurements needs to be considered when categorizing a patient according to the C-EOS, and it is essential in repeated measurements on the same patient, as with the APR [8].

Etiology

Our study confirms the findings by Cyr et al. with an overall substantial inter-rater agreement. Assessment of etiology depends on the case text provided to the raters and bias the results towards a higher agreement. Therefore, the primary author who summarized the cases did not participate in the ratings. We included descriptions of neurological examination and CT/MRI findings which is an essential part of the evaluation of patients with EOS [19]. Raters were also familiar with the original work by Williams et al. in which a priority order for the classification of etiology was stated [1]. Nevertheless, in only 76% of cases, all 4 raters agreed on the etiology. A case by case review showed specifically two issues of disagreement. Firstly, patients with syndromes and/or chromosome abnormalities were the main reason for disagreement, as also suggested in the original study [1]. For example, Goldenhar and Klippel-Feil syndromes are mentioned as syndromic etiologies; however, they are characterized by structural abnormalities of the spine and, thus, should strictly be classified as congenital/structural [1,20]. Secondly, cases with neural axis abnormalities such as syringomyelia with no neurological deficits were classified as either neuromuscular or idiopathic.

Table 3. Accuracy of major curve angle, kyphosis and APR in early-onset scoliosis assessed with standard error of measurement (SEM) and 95% limits of agreement (LOA)

	Inter-rater SEM	Inter-rater LOA	Intra-rater SEM	Intra-rater LOA
Major curve angle, °				
Overall	4.6	12.8	4.0	11.1
Congenital/ structural	4.5	12.4	4.4	12.2
Neuromuscular	6.9	19.1	5.2	14.5
Syndromic	3.4	9.4	2.6	7.2
Idiopathic	3.1	8.5	2.9	8.1
Kyphosis, °				
Overall	7.4	20.6	6.2	17.3
Congenital/ structural	8.4	23.4	6.9	19.0
Neuromuscular	8.3	22.9	6.0	16.5
Syndromic	7.2	20.1	7.2	20.0
Idiopathic	5.5	15.3	4.8	13.3
APR, °/year*				
Overall	6.3	17.4	5.3	14.7
Congenital/ structural	5.5	15.3	4.6	12.8
Neuromuscular	10.0	27.6	8.0	22.2
Syndromic	4.1	11.5	4.1	11.2
Idiopathic	4.2	11.7	3.9	10.8

*Annual progression rate

Neural axis abnormalities are present in approximately 20% of presumed idiopathic EOS patients [20,21], but mentioned as possible neuromuscular etiologies [1]. A clarification of these issues could increase the reliability of etiology even further. Moreover, the clinical use of the classification could be improved if patients were grouped according to the treatment strategy.

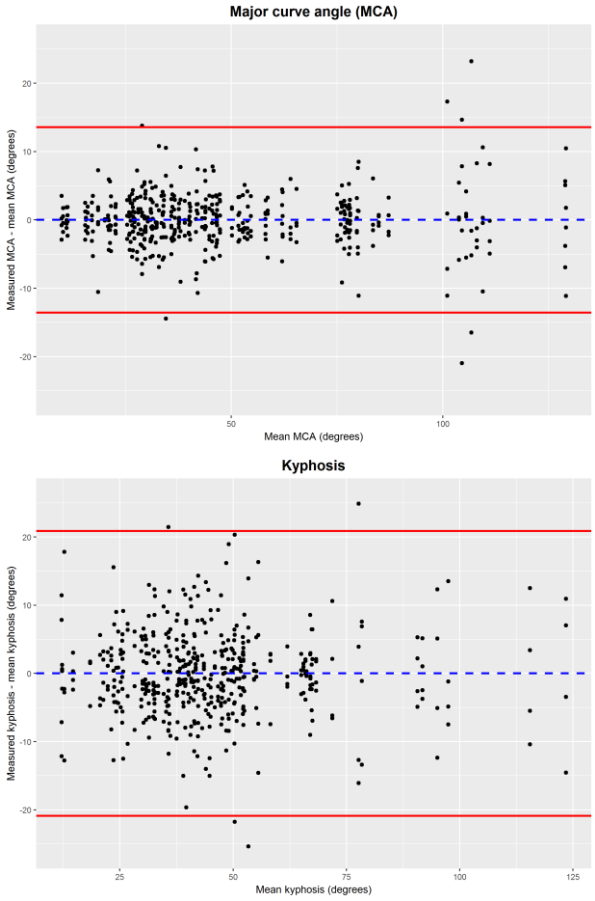

Figure 3a and 3b. Inter-rater modified Bland-Altman plots illustrating the variability in measurements of major curve angle (Figure 3a) and kyphosis (Figure 3b) according to Jones et al [140]. Each dot represents a single rater's measurement plotted against the mean of all measurements for the individual patient. The red lines indicate upper and lower 95% limits of agreement.

Major curve angle

Reliability assessed with ICC was, as expected, excellent due to the large variation within the study population. The kappa coefficient for both ratings were lower than previously reported [1,7]. The reason for this is probably that raters in this study measured MCA on radiographs rather than rating them from a written text. Nevertheless, kappa coefficients showed almost perfect agreement. More importantly, the measurement error, or accuracy, of measuring MCA was calculated. A systematic review by Langensiepen et al. [22] on the reproducibility of Cobb´s method in idiopathic scoliosis reported somewhat lower values of intra- and inter-rater SEM than our study. However, pre-selection of end vertebra, differences in observer training, limited populations (Cobb angles 20-50°) and inclusion of only idiopathic curves might underestimate true measurement errors. Moreover, a wide range of statistical methods were reported making comparisons difficult [22]. With no pre-selected end vertebra or endplates, we find the variability in our study more representative of a clinical setting. The measurement error is presumably larger in EOS compared to AIS. Loder et al. found inter-rater LOA of 7.3° for non-congenital EOS with pre-selected end vertebra [23]. Numbers are higher for congenital (11.8°) and neuromuscular (14.8°) scoliosis [24,25]. The 12.8° LOA in this study represents the value by which there is a 95% probability of a true difference in MCA between two raters in patients with EOS regardless of etiology. The LOA in our study for each etiology correspond with the above-mentioned studies [23–25]. These differences in measurement error depending on the etiology need to be considered when using the C-EOS and in the clinical setting.

Kyphosis

The reliability of kyphosis has previously been reported to be lower than for MCA in patients with AIS [14]. As with MCA, the reliability of kyphosis is better with pre-determined vertebrae than for a non-fixed kyphosis [15]. In the C-EOS, kyphosis is "the maximum measurable kyphosis between any two levels" [1]. Consequently, we would expect to see poorer reliability of kyphosis

in our study. Expectations were met, as all 4 raters agreed in 56% of cases and reliability assessed with Fleiss kappa was moderate. Still, ICC for kyphosis was good, reflecting the wide range of kyphosis in the population. This discrepancy can be explained by the relatively large overall LOA for kyphosis in our study. LOA for kyphosis in idiopathic patients was only slightly larger than the LOA for kyphosis reported in AIS (13°) [15], and for neuromuscular patients comparable to previously reported accuracy (24°) [25]. The considerable measurement error for kyphosis in EOS found in this study needs to be accounted for when using the C-EOS.

APR

According to the measurement error for MCA described previously, any progression less than 13° could be attributed to measurement error and does not necessarily represent actual curve progression. This is greater than the 10°/year increments proposed in the classification system. The larger measurement error for APR compared to MCA was expected, as the measurement error on both the first and second MCA measurement affects the APR. As APR depends on the time between measurements, shortening the time-interval will consequently increase the measurement error. This could be addressed by calculating APR based on 3 or more radiographs, or by extending the time-interval between measurements to a minimum of 1 year.

This is, to our knowledge, the first study to report measurement errors for MCA and kyphosis in an EOS-only population including all etiologies. Although we cannot assess the exact causes for the generally larger measurement errors for EOS compared to AIS with this study, the reasons probably include poorly defined endplates (young age and/or structural deformities), local kyphosis/gibbus deformity and larger curves with greater rotational deformity (Figure 2).

We used a semi-automatic categorization of continuous variables to rule out misclassifications due to rough approximations or simple errors as otherwise described in the original study by Williams et al [1]. Hence, the results represent the consistency in measurements between raters and as such not the agreement in classification of the continuous variables. We have reported various statistical methods for assessing reliability and agreement which allows comparison with both previous and future studies, and more detailed describe the challenges when using the C-EOS.

A previous systematic review suggested that the results of reproducibility studies are a consequence of the chosen method of assessment [22]. Consequently, the accuracy of our results may well have been influenced by the software for imaging and measurements. The results are based on raters and patients from a single center which could potentially increase the consistency in ratings. We do however find our results representative of an EOS population.

Conclusion

We found substantial agreement for etiology; however, disagreement was found for syndromic patients or patients with neural axis abnormalities. The reliability of MCA was excellent, however somewhat lower for kyphosis and APR with less accuracy in measurements. The measurement errors of MCA, kyphosis and APR depended on the etiology, to a large extend. The LOA for APR was larger than the 10°/year increments proposed in the C-EOS, suggesting that APR should be based on 3 or more radiographs, or the time-interval between measurements should be a minimum of 1 year.

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Appendix 1

Cases
9-year old girl with no underlying disease or comorbidity. Normal neurological examination and MRI with no intraspinal pathology.
15-year old girl diagnosed at 8 years of age known with idiopathic thrombocytopenia. Normal neurological examination. MRI not available
12-year old boy diagnosed with hemivertebra at Th4, otherwise healthy. Normal neurological examination. MRI showing multiple cervical vertebral malformations but no intraspinal pathology.
15-year old girl followed since she was 6-year-old. No underlying disease, normal neurological examination and MRI with no intraspinal pathology.
10-year old girl with chromosome 4q21 deletion born with ventricular and atrial septal defect, heart surgery 4 months old, epilepsy, macrocephaly, small hands and mental retardation. Neurological examination with spasticity in extremities. MRI not available.
11-year old girl diagnosed at 4 years of age. No underlying disease, normal neurological examination and MR with no intraspinal pathology
10-year old boy with chromosome 15 micro duplication, epilepsy, mental retardation, developmental disorder and recurrent pneumonia. Neurological examination with spasticity of lower extremities. MRI with agenesis of the corpus callosum, no spinal malformations or intraspinal pathology.
15-year old girl with Rett's syndrome followed since she was 6-year-old. Multiple lung infections, wheelchair dependent and no walking ability. MRI not available.
16-year old boy followed with hemivertebra and no other illness. Normal neurological examination. CT and MRI with lumbalization of S1, left sided hemivertebra L5/S1, right sided hemivertebra L3, no intraspinal pathology.
12-year old boy with Arnold Chiari malformation and syrinx, treated with neurosurgical decompression as 6-year-old. Normal neurological examination. MRI with prominent syrinx in medulla and signs of earlier fossa posterior decompression.
8-year old girl with block vertebra and cloacal atresia, repeated surgery for the cloacal abnormalities. Normal neurological examination. CT with fused vertebra L2-L4 on right side and fusion L4-L5 on left side. MRI with no intraspinal pathology.
5-year old boy with hemivertebra, no other illness. Normal neurological examination, CT with hemivertebra L2/L3 and L4, MRI with no intraspinal pathology.
11-year old girl with hemivertebra, no other illness. Normal neurological examination and MRI with no intraspinal pathology.
12-year old boy with cerebral palsy and tetraplegic spasticity treated with intrathecal baclofen pump. MRI with no intraspinal pathology.
10-year old girl with tuberous sclerosis and epilepsy, normal neurological examination. MRI with no intraspinal pathology.
15-year old boy with chromosome 17q21 deletion followed since 4 years of age, anisomelia, retentio testis, leg length discrepancy and mental retardation. Normal neurological examination and MRI with no intraspinal pathology.
6-year old boy with Marfan syndrome and aortic root dilation, no former heart surgery. Normal neurological examination, MRI not available.
8-year old boy with Cri du Chat syndrome due to chromosome 5p deletion also diagnosed with mental retardation. Normal neurological examination and MRI with no intraspinal pathology.
9-year old girl with cerebral palsy and multiple lung infections. Neurological examination shows spasticity with athetotic movements of the upper extremities. MRI not available.

8-year old boy with spinal muscular atrophy type II, recurrent pneumonia and daily CPAP. Wheelchair dependent. MRI not available.
4-year old boy with dyssegmental dysplasia, tracheostomized with multiple lung infections, urge incontinence and walking disabled. CT and MRI with platyspondyly and several split vertebral bodies, narrow thoracic spinal canal.
11-year old boy diagnosed at 4 years of age. Normal neurological examination, MRI with Arnold Chiari malformation type 1 and persistent syringomyelia from C5-Th11, but regression of herniated cerebellar tonsils. Arnold Chiari malformation and Syringomyelia treated conservatively without neurosurgical intervention.
13-year old girl with Spinal Muscular Atrophy type II, low body weight and recurrent pneumonia. Neurological examination with spastic extremities. MRI not available.
4-year old boy with hemivertebra and no other illness. Normal neurological examination, CT with L3 hemivertebra, MRI not available.
8-year old boy with hemivertebra. No other illness and normal neurological examination. CT and MRI with hemivertebra but no intraspinal pathology.
5-year old boy with Goldenhar syndrome, hydrocephalus and bilateral microtia. Normal neurological examination. CT with lumbosacral hemivertebra and anterior fusions from L4 to S1, MRI with stationary cervical hydromyelia, thoracic syrinx and widened spinal channel.
6-year old boy with hemivertebra and no other illness. Normal neurological examination and CT with hemivertebra L3/L4, MRI with no intraspinal pathology.
8-year old girl with unilateral multicystic kidney, decreased lung function and recurrent pneumonia. Normal neurological examination. CT with multiple vertebral anomalies, MRI with no intraspinal pathology.
7-year old girl with no underlying disease or comorbidity. Normal neurological examination. CT and MRI with thoracic butterfly vertebra and L3-L4 block vertebra, no intraspinal pathology.
6-year old girl with VACTERL association with esophageal atresia, surgically treated ventricular septal defect and recurrent airway infections. Normal neurological examination. CT with fusion anomalies and thoracolumbar hemivertebra.
10-year old girl diagnosed at 5 years of age. No underlying disease or comorbidity. Normal neurological examination. CT with no vertebral abnormalities and MRI with no intraspinal pathology.
3-year old boy with flat foot and no other illness. Normal neurological examination and MRI with no intraspinal pathology.
5-year old boy with hemivertebra born with esophageal atresia and tracheoesophageal fistula resulting in recurrent pneumonias. Persistent ventricular septum defect in infancy and finger anomalies on the right hand. CT shows a hemivertebra at the L4 level.
10-year old girl diagnosed with deformity and Arnold Chiari type 1 malformation with severe syringomyelia at the age of 7. Neurosurgical occipitocervical decompression. Normal neurological examination and latest MR with changes following occipitocervical decompression and regression of the syringomyelia from C5-Th9.
4-year old boy with Beckwith-Wiedemann syndrome due to a chromosome translocation, no other illness. Normal neurological examination MRI not available.
8-year old boy with no underlying disease and no prior medical history. Normal neurological examination and MRI not available.
7-year old girl with Beckwith-Wiedemann syndrome, no other illness. Normal neurological examination, MRI not available.
8-year old boy with block vertebra, born with imperforate anus and treated with surgery in infancy. Mild mental retardation, normal neurological examination. CT and MRI not available.
10-year old girl diagnosed at 8 years of age. No underlying disease or comorbidity and normal neurological

examination. MRI without intraspinal pathology.
11-year old girl diagnosed at 8 years of age. No underlying disease, normal neurological examination and MRI with no intraspinal pathology.
8-year old girl with no underlying disease, normal neurological examination and MRI with no intraspinal pathology.
2-year old boy with achondroplasia and multiple upper airway infections. Normal neurological examination. MRI with hydrocephalus, cervical spinal stenosis, hydromyelia Th3-Th10 and wedging of L1.
6-year old boy with hemivertebra. No other illness and normal neurological examination. MRI not available.
9-year old girl with no underlying disease or comorbidity. Normal neurological examination and MRI with no intraspinal pathology.
12-year old boy diagnosed as 6-year-old. Besides, diagnosed with migraine. Normal neurological examination. MRI not available.
6-year old boy with no underlying disease. Normal neurological examination and MRI with no intraspinal pathology.
7-year old girl born with widened eye slit and diagnosed with mental retardation, developmental disorder and recurrent pneumonia. Normal neurological examination and MRI with no intraspinal pathology.
5-year old girl with ADHD and no other illness. Normal neurological examination and MRI with no intraspinal pathology.
9-year old girl with no underlying disease. Normal neurological examination and MRI not available.
11-year old girl with atrial septal defect treated with intravascular device, followed since she was 9. Normal neurological examination. MRI with hydromyelia from Th5-Th8.
6-year old girl with Soto syndrome, patent ductus arteriosus surgically treated in infancy, recurrent airway infections and mental retardation. Neurological examination with normal motor function and dyspraxia. MRI not available.
1.5-year old boy with hemivertebra and no other illness. Normal neurological examination. CT with hemivertebra Th11/Th12 and spina bifida L4-L5. MRI not available.
8-year old boy with no underlying disease or comorbidity. Normal neurological examination. MRI and CT with spina bifida on the lowest levels with multiple lumbosacral deformities.
3-year old girl with VACTERL association, esophageal atresia surgically treated through thoracotomy. Normal neurological examination, MRI not available.
6-year old girl with chronic hip dislocation despite surgery. Neurological examination with unstable gait using bilateral ankle foot orthosis. MRI with sacral dysplasia, L5-S1 dysraphism, tethered cord at conus medullaris and small lumbar syrinx.
11-year old boy with Prader-Willis syndrome treated with growth hormone. No comorbidity. Normal neurological examination, MRI not available.
11-year old boy diagnosed at the age of 9. No underlying illness or comorbidity. Normal neurological examination and MRI with no intraspinal pathology.
9-year old boy with hemivertebra and urethral stricture. Normal neurological examination. MRI with hemivertebra Th11 and butterfly vertebra Th6, no intraspinal pathology.
10-year old girl with no underlying disease or comorbidity. Normal neurological examination. CT with no vertebral abnormalities and MRI with 6 x 2 mm syrinx from C2-C6.
10-year old boy with Arnold Chiari type 1 malformation, no other illness. Neurological examination with slightly decreased abdominal reflexes on the left side, normal gait and normal reflexes and motor function in lower extremities. MRI with Chiari type 1 malformation and large syringomyelia with septae in the total length of the medulla.

Paper II

Use of a distraction-to-stall lengthening procedure in magnetically controlled growing rods: A single-center cohort study.

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Use of a distraction-to-stall lengthening procedure in magnetically controlled growing rods: A single-center cohort study

Benny Dahl[1], Casper Dragsted[2], Søren Ohrt-Nissen[2], Thomas Andersen[2] and Martin Gehrchen[2]

Abstract

Purpose: The objective of this study was to assess the outcome of patients treated with magnetically controlled growing rods (MCGRs) using a standardized distraction procedure with intended distraction-to-stall and to compare the outcomes between idiopathic and nonidiopathic patients. **Methods:** This was a retrospective single-center cohort study. Conversion cases were excluded. Distractions were performed with 2- to 3-month intervals with the intention of distraction-to-stall on both rods. Distraction length was measured on X-rays every 6 months. Spinal height was assessed using T1-T12 and T1-S1 annual increase. **Results:** 19 patients (eight idiopathic and 11 nonidiopathic) were included. Mean age at surgery was 9.7 $\pm$ 1.9 years, and median follow-up was 1.9 years (interquartile range (IQR): 1.3–2.2). Major curve improved from median 76° (IQR: 64–83) preoperatively to 42° (IQR: 32–51) postoperatively ($p < 0.001$) corresponding to a curve correction of 43% (IQR: 33–51). Correction was maintained at 1- and 2-year follow-up. Median annual T1-T12 and T1-S1 height increase were 10 mm (IQR: 6–16) and 11 mm (IQR: 7–33), respectively. A total of 159 distraction procedures were performed; 83.5% of these were distracted-to-stall, and 16.5% were stopped due to discomfort. Median rod distraction per procedure was 2.0 mm (IQR: 1.6–2.7) for the concave side and 1.7 mm (IQR: 1.4–2.5) for the convex side. Five patients had implant-related complications. Patients with nonidiopathic etiology were significantly younger and had lower flexibility compared with idiopathic patients ($p \leq 0.040$). However, we found no statistically significant difference in curve correction, spinal height increase, distraction length, or complications between the two groups ($p \geq 0.109$). **Conclusion:** MCGR effectively corrected the deformity and increased spinal height using a distraction procedure with intended distraction-to-stall. Five of 19 patients had implant-related complications, and we found no difference in the outcomes between idiopathic and nonidiopathic patients.

Keywords

distraction, early onset scoliosis, growth, magnetically controlled growing rods, orthopedics, PAEDS, scoliosis, spine

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Introduction

Magnetically controlled growing rod (MCGR) surgery is a recently developed technique for treating early-onset scoliosis (EOS). EOS is defined as scoliosis diagnosed before the age of ten,[1] and if left untreated, EOS is associated with increased mortality.[2] The patients often have a substantial remaining skeletal and pulmonary growth potential, and therefore, the main goal of treatment is to halt curve

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progression while allowing spinal growth to preserve pulmonary function.[3] Bracing and casting are first choices as they allow continuous growth of the spine and can delay final surgery.[4] However, in patients with curve progression, despite bracing, surgery may be indicated.[3] Because early thoracic fusion can lead to a restrictive decreased lung function,[5,6] different growth-friendly surgical techniques have been developed.[7] Traditional growing rods are a distraction-based technique that corrects the deformity and prevents curve progression,[8] but it requires repetitive surgical procedures leading to high complication rates.[9] To avoid repeated surgical procedures, the MCGR system was developed allowing lengthening with an external remote control (ERC).[10–12] Preliminary results are promising as the MCGR procedure corrects the deformity while allowing continuous growth of the spine. However, despite reducing the number of surgical procedures compared with traditional growing rods,[13,14] the rate of implant-related complications remains high.[13–16]

Consensus is lacking regarding distraction frequency, amount, and technique.[17] Different distraction protocols have been described where the desired distraction length is based on estimated growth ("tail-gating") or a set distraction amount and monitored with X-ray or ultrasound measurements.[16,18–22] No studies so far have described the use of a distraction procedure with intended distraction-to-stall (distraction to "clunking") and not relying on a set distraction amount or estimated growth.

The primary purpose of this study was to assess curve correction and complications in patients operated with MCGR and to evaluate the efficacy of a standardized distraction procedure. The secondary purpose was to compare the outcomes for idiopathic patients with that of nonidiopathic patients.

Materials and methods

We conducted a retrospective study on all patients surgically treated with MCGRs at a single institution. Patients were prospectively registered from November 2013 through August 2017. Exclusion criteria were single-rod constructs or conversion cases with former growth instrumentation. Age at diagnosis was registered, and etiology was recorded according to the Classification of Early-Onset Scoliosis (C-EOS).[1] A total of 21 patients were treated with MCGR in the study period. Two were excluded from the study as they were converted from former growth instrumentation. Mean age at index surgery was 9.7 years (SD: 1.9, range: 6.2–12.7), and median follow-up was 1.9 years (inter quartile range (IQR): 1.3–2.2, range: 0.3–3.6); 17 patients had minimum 1-year radiological follow-up. The study was approved by the local health authorities and data protection agency (journal no.: 2012-58-0004).

Surgical procedure

All patients underwent surgery with two attending spine surgeons through a posterior-only approach according to the technique described by Akbarnia et al.[10] Initially, the patients received two standard rods. Later in the study period, we used one standard rod on the concave side of the major curve and one offset rod on the convex side. Primary intended fixation method for proximal and distal anchor sites was pedicle screws; this could be changed at the discretion of the treating surgeon in case of poorly developed pedicles or similar. Likewise, the use of cross-links was at the discretion of the treating surgeon. Facetectomies were performed on the fixation levels, and local bone tissue mixed with bone substitute was used for fusion. In the majority of procedures, the rods were passed intramuscularly in the craniocaudal direction to avoid surgical exposure between the cranial and caudal fixation levels. The distraction ability of the rods was manually tested before insertion and after any contouring of the rods. We intended to achieve maximal correction with primary surgery respecting overall balance; hence, maximal distraction was applied on both rods intraoperatively. Postoperative bracing was used in selected cases at the discretion of the surgeon.

Distraction procedures

Distractions were mainly performed in an outpatient clinic setting with the patient in a prone position or lying on the side and without the need for pain killers or sedation. All distractions were performed by one of two experienced spine surgeons in a standardized approach with the intention of distracting-to-stall, also referred to as "clunking" or rod slippage. The two actuators were identified with a magnet, and distractions were performed on each rod separately, starting on the concave side of the major curve. If further distraction on the concavity could be achieved, a second lengthening on the concavity was attempted as a third step. The procedure was interrupted before clunking if the patient expressed discomfort or showed signs of such. Distractions were categorized as not specified if information of distraction stop was insufficient. First distraction was performed 3 months after the index surgery. Distractions were generally performed with 2- to 3-month intervals and achieved lengthening monitored with full-spine X-rays every half a year. For patients with congenital/structural etiology, a shorter distraction interval was preferred in the beginning of the treatment. Distraction interval was recorded as number of days since last intervention, either surgery or distraction.

Radiological assessment

Radiographs were obtained in the international Digital Imaging and Communications in Medicine format and

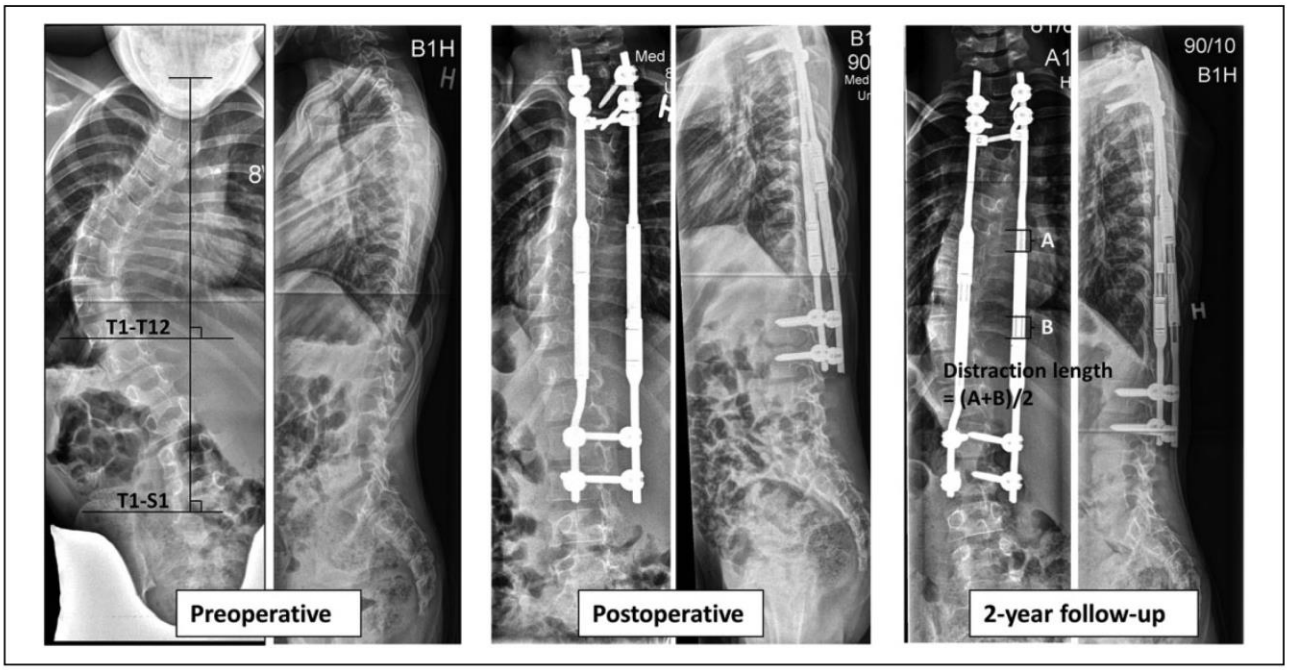

Figure 1. A case showing an 8-year old boy with Cri-du-chat syndrome. Progression despite Boston bracing. Major curve improved from 75° preoperative to 32° postoperative and was 37° at 2-year follow-up. Kyphosis was 22°, 14°, and 16°, respectively. T1-T12 and T1-S1 annual growth values were 14 and 22 mm/year, respectively.

uploaded to the validated online imaging system KEOPS (SMAIO, Lyon, France)[23] where radiographic measurements were performed. Radiographs were taken in the most upright position preoperatively and postoperatively; at 3, 6, and 12 months postoperatively, and onward every 6 months. On coronal radiographs, the following variables were recorded: major curve and secondary curve angle (defined as the largest secondary curve >20°), supine lateral bending major curve, coronal balance (the horizontal distance from the C7 plumb line to the central sacral vertical line), and upper and lower instrumented level. A preoperative annual progression rate (APR) was calculated according to the C-EOS.[1] On sagittal radiographs, kyphosis was recorded as the maximum Cobb angle between any two vertebrae in consistency with the C-EOS. Lordosis was recorded as the underlying Cobb angle to S1. From coronal measures, the following were calculated and expressed in percentages as described in former studies[24,25]:

$$\text{Curve flexibility} = \frac{\text{Preoperative major curve angle} - \text{bending major curve angle}}{\text{Preoperative major curve angle}}$$

$$\text{Curve correction} = \frac{\text{Preoperative major curve angle} - \text{postoperative major curve angle}}{\text{Preoperative major curve angle}}$$

$$\text{Curve correction Iindex (CCI)} = \frac{\text{Curve correction (\%)}}{\text{Curve flexibility (\%)}}$$

Thoracic (T1-T12) and total spine (T1-S1) heights were measured preoperatively and postoperatively and at the latest radiological follow-up prior to final fusion surgery in accordance with former studies[13] (Figure 1). Annual T1-T12 and T1-S1 height gain were calculated together with T1-T12 and T1-S1 height gain per distraction procedure. All images were calibrated with the known rod diameter ensuring consistency in the measurement and comparison of multiple radiographs. Rod distractions were assessed on radiographs and measured on each rod separately not taking into account the distraction performed intraoperatively (Figure 1). A yearly distraction and a per-procedure distraction length were calculated.

Statistics

Statistical analyses were performed using R, version 3.2.5. Distributions were assessed with histograms and quantile–quantile plots. Data are presented as proportions (%), means with standard deviation (SD) or medians with range or IQR. Repeated measures of slot length are presented in Spaghetti plots and radiographic outcomes in boxplots. Categorical data were compared using Fisher's exact test and continuous data with two-tailed Student's *t*-test or Wilcoxon's test.

Results

Median preoperative APR was 14.4° (IQR: 7.4–18.9), and median flexibility was 37.0% (IQR: 24.4–51.4). Major curve and secondary curve were reduced from 76° (IQR: 64–83) and 44° (IQR: 37–52) preoperative to 42° (IQR: 32–51) and 32° (IQR: 22–40) postoperative, respectively

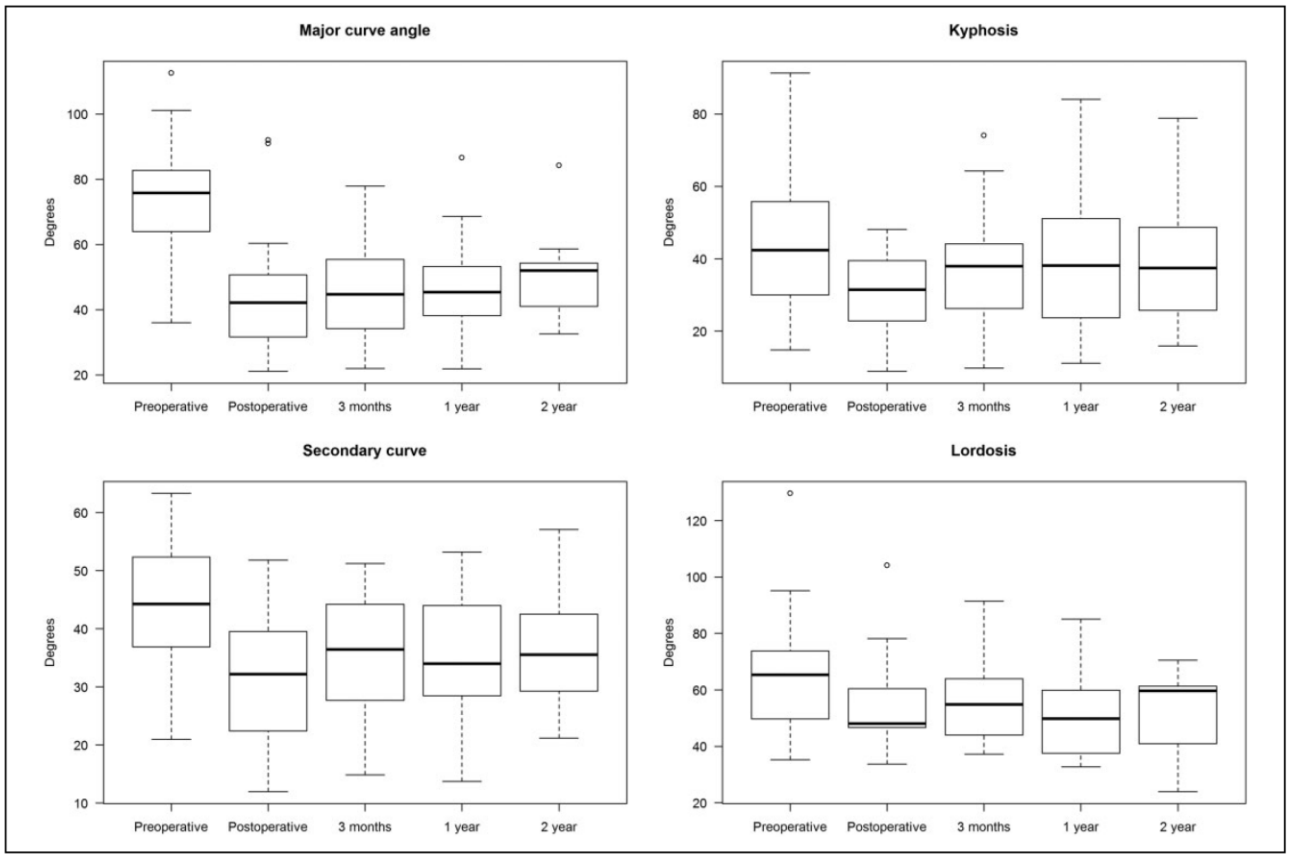

Figure 2. Boxplot of major curve angle, overall kyphosis, secondary curve, and lordosis. 17 patients were available for 1-year follow-up and 11 patients for 2-year follow-up.

($p < 0.001$). This corresponded to a median major curve correction of 43% (IQR: 33–51) and a median CCI of 108% (IQR: 91–117). Correction was maintained throughout the distraction period. Compared with preoperative values, median major curve was 45° (IQR: 34–55) at 3-month, 45° (IQR: 38–53) at 1-year, and 52° (IQR: 41–54) at 2-year follow-ups ($p < 0.001$). Likewise, secondary curve was 36° (IQR: 28–44) at 3-month, 34° (IQR: 29–44) at 1-year, and 36° (IQR: 29–43) at 2-year follow-ups ($p < 0.006$; Figure 2). Kyphosis was significantly reduced from 42° (IQR: 30–55) preoperative to 32° (IQR: 23–40) postoperative ($p < 0.001$); however, we found no statistically significant difference compared with preoperative values at 3-month (median: 38°, IQR: 27–44), 1-year (median: 38°, IQR: 24–50), or 2-year (median: 37°, IQR: 26–49) follow-ups ($p > 0.168$; Figure 2). No difference was found regarding coronal balance ($p > 0.441$; Figure 2).

Five patients had implant-related complications (three screw loosening, one rod breakage, and one iliac hook fixation failure). This led to four unplanned reoperations as one patient with screw loosening and proximal junctional kyphosis (PJK) was handled conservatively (Figure 3). Additionally, one patient underwent unplanned surgery due to distal adding on and pelvic obliquity, and further, one patient had a revision surgery as full distraction was reached after 23 months. Mean T1-T12 and T1-S1 height increased from 186 mm (SD: 31) and 301 mm (SD: 46) preoperatively to 207 mm (SD: 28) and 339 mm (SD: 43) postoperatively, respectively.

A total of 159 distractions were performed during the study period; 83.5% were distracted to stall (Table 1). We saw only positive gains in distraction length indicating no cases with loss of distraction (Figure 4). Two distractions were performed in short general anesthesia. One distraction led to persistent pain in a patient where the actuator was reversed in an additional procedure.

Eight patients were characterized as idiopathic according to the C-EOS (Table 2). Patients with nonidiopathic etiology were significantly younger and had lower flexibility compared with idiopathic patients ($p \leq 0.040$). We found no statistically significant difference in CCI, spinal height increase, distraction length, or complications between the two groups ($p \geq 0.109$; Table 3).

Discussion

In a single-center cohort of mainly EOS patients, we demonstrate the efficacy of MCGR to correct deformity and maintain curve correction through the distraction period. A standardized distraction procedure with intended

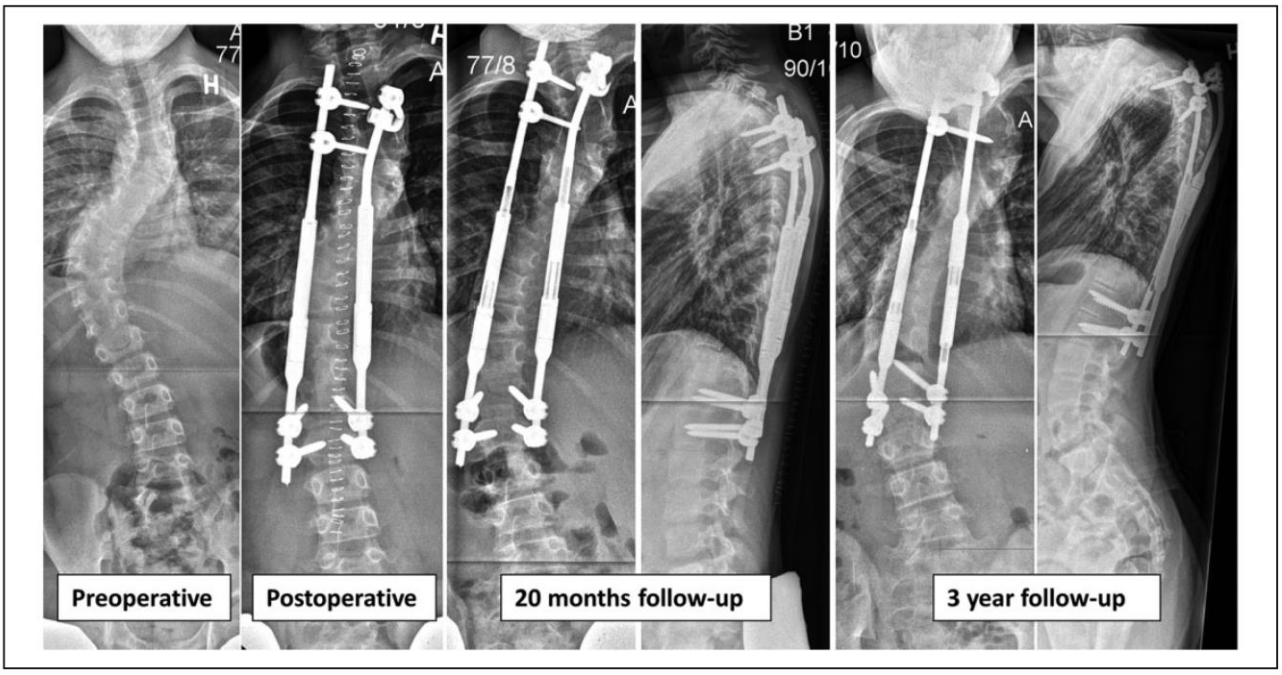

Figure 3. A case showing a 9-year old boy with neurofibromatosis type 1. Progression despite Boston bracing. Preoperative major curve of 72° was reduced to 42° postoperatively. At 1-year follow-up, a CT scan showed proximal screw loosening on the right rod, but symptoms disappeared, and distractions were continued until full distraction at 20-month follow-up. After replacement of the rods, the patient developed proximal junctional kyphosis and hook displacement, and final fusion was performed 3 years after initial implantation. CT: computed tomography.

Table 1. Distraction procedures.

	Total $n = 159$
T1-T12 annual increase, mm/year[a]	10 [6, 16] (−2, 46)
T1-S1 annual increase, mm/year[a]	11 [7, 33] (0, 63)
Concave rod distraction, mm/year[a]	10.3 [6.4, 12.9] (4.1, 30.5)
Convex rod distraction, mm/year[a]	8.2 [6.8, 11.6] (3.5, 19.5)
Concave rod distraction, mm/procedure[a]	2.0 [1.6, 2.7] (0.9, 7.6)
Convex rod distraction, mm/procedure[a]	1.7 [1.4, 2.5] (0.6, 4.8)
Distraction stop, *n* (%)	
Discomfort	26 (16.5)
Stall	132 (83.5)
Not specified	1
Distraction interval, days[a]	73 [62, 92] (17, 199)

[a]Median [interquartile range] (range).

distraction-to-stall ensured spinal growth throughout treatment without increasing the complication rate compared with results reported in the literature. We found no difference in radiographic or clinical outcomes between patients with idiopathic and nonidiopathic deformities.

The overall goal of surgical treatment is to preserve lung function by allowing continuous growth of the spine and secondarily to reduce pain and improve quality of life for these children. As such, the timing of surgery relies on two main indicators: a severe curve or curve progression despite bracing and an estimated substantial remaining growth potential. Various inclusion criteria are listed in previous studies of MCGRs.[10,11,14–16,18,20,26–29] Age at index surgery and etiology in our study did not differ considerably from these. Some studies have indicated that single-rod MCGR constructs and conversion from former growth instrumentation are associated with higher complication rates, poorer curve correction, and less spinal growth.[10,18,22,26,29] For these reasons, we excluded these patients from our study.

Median curve correction in our study was comparable to other studies (range: 34–57%).[10,15,16,20,24,26,28,30] The surgical technique is inconsistently reported in these studies, and whether to perform maximal intraoperative distraction and curve correction is unknown. The concern is increased rod loading and the risk of early distraction failure or complications.[17] However, we performed maximal intraoperative distraction and experienced no distraction failures throughout the distraction period. Secondary curve was also reduced postoperatively, and so far, this is the first study to report results on the secondary curve with MCGRs.

Several studies show a tendency similar to our study with a reduction of kyphosis after surgery and a small increase during the distraction period.[10,11,18,24,28,29] Akbarnia et al. hypothesized that increased overall kyphosis at follow-up was a result of increasing kyphosis outside the instrumented levels.[10] Rod contouring is limited around the actuator portion of the MCGR. Consequently, surgery results in a relative hypokyphosis at the instrumented

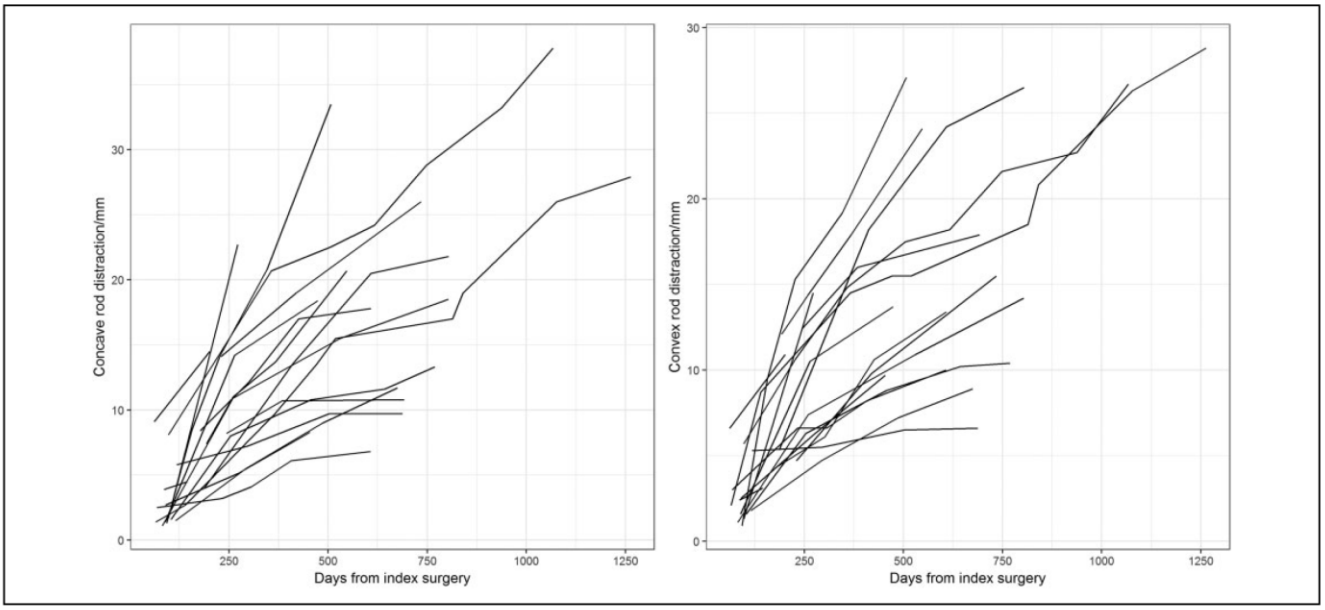

Figure 4. Spaghetti plots showing distraction length throughout the distraction period on the concave and convex rod, respectively.

Table 2. Demographics.

	Total $n = 19$
Age at surgery, years[a]	9.7 (1.9)
Age at diagnosis, years[a]	6.0 (2.6)
Male sex, *n* (%)	10 (53)
ASA classification, *n* (%)	
1	7 (36.8)
2	4 (21.1)
3	8 (42.1)
Height, cm[a]	137.1 (15.4)
Weight, kg[a]	28.7 (9.1)
C-EOS etiology, *n* (%)	
Congenital/structural	3 (15.8)
Idiopathic	8 (42.1)
Neuromuscular	5 (26.3)
Syndrome	3 (15.8)
Major curve location, *n* (%)	
Thoracic	17 (89.5)
Lumbar	2 (10.5)
Prior treatment, *n* (%)	
Full-time brace	12 (63.2)
Nighttime brace	4 (21.1)
None	3 (15.8)
Indication for surgery, *n* (%)[b]	
Brace intolerance	1 (5.3)
Curve progression	14 (73.7)
Decreasing lung function	2 (10.5)
Major curve angle >60°	7 (36.8)
Pain	2 (10.5)
Pelvic obliquity	1 (5.3)
Thoracic curve, brace inapplicable	2 (10.5)

ASA: American Society of Anesthesiologists.
[a]Mean (standard deviation).
[b]Totals exceed 100% as some patients had more than one indication.

levels, which leads to a compensatory kyphosis on top of the instrumentation. It may lead to PJK and associated proximal implant fixation failure.[29] This was probably the case for one patient in our study with a high thoracic major curve who underwent revision and subsequently final fusion addressing this issue (Figure 3). Two patients with distal screw loosening were more likely to be caused by suboptimal screw positioning at implantation. The rod fracture occurred in a patient with congenital fusion anomalies and hyperlordosis weighing 17 kilograms at implantation with 4.5-mm rods so no conclusions can be drawn from this. Overall, the rate of implant-related complications and unplanned surgery in our cohort was comparable to other studies[14,16,18,20,26,28] and with no deep infections.

Based on the results reported by Dimeglio et al., the normal spine growth has been established. The T1-T12 height increases with 0.7 cm/year from 5 to 10 years of age and 1.1 cm/year during puberty. T1-S1 height increases with 1 cm/year from 5 to 10 years of age and 1.8 cm/year between 10 years of age and skeletal maturity.[31] Compared with this, T1-T12 and T1-S1 annual increases in our study were satisfying, however, with a wide range. Other studies using a distraction protocol relying on expected growth and ERC measurements report T1-T12 and T1-S1 height increase rates of 3.6–9.6 and 6.3–10.6 mm/year, respectively.[15,27–29] Only one patient in our cohort had no increase in spinal height despite rod distractions were successful (T1-T12 was −2 mm/year), most likely due to PJK (Figure 3). This case underlines that sagittal deformity needs to be taken into consideration when assessing spinal height on an anterior–posterior radiographs.

Table 3. Idiopathic vs. nonidiopathic etiology.

	Nonidiopathic ($n = 11$)	Idiopathic ($n = 8$)	p-Value
Age index surgery, years[a]	8.9 (1.5)	10.8 (1.9)	0.040
Preoperative major curve angle, degrees[b]	76 [69, 87]	70 [59, 80]	0.492
Preoperative kyphosis, degrees[b]	37 [29, 59]	43 [39, 51]	0.965
Preoperative APR, degrees/year[b]	15 [12, 20]	8 [7, 15]	0.328
Flexibility, %[b]	24 [24, 36]	46 [40, 52]	0.036
Curve correction, %[b]	33 [20, 49]	47 [46, 50]	0.091
Correction index, %[b]	98 [88, 133]	109 [96, 112]	0.815
Number of levels fused[b]	14 [13, 16]	12 [11, 12]	0.001
T1-T12 annual increase, mm/year[b]	11 [6, 16]	9 [6, 19]	0.741
T1-S1 annual increase, mm/year[b]	12 [9, 33]	10 [6, 26]	0.591
Concave rod distraction, mm/year[b]	11.8 [7.5, 18.0]	8.2 [6.0, 11.1]	0.182
Convex rod distraction, mm/year[b]	9.2 [7.8, 14.1]	7.2 [5.7, 8.9]	0.109
Concave rod distraction, mm/procedure[b]	2.4 [1.6, 2.7]	1.7 [1.5, 2.6]	0.423
Convex rod distraction, mm/procedure[b]	1.8 [1.6, 3.0]	1.6 [1.3, 1.9]	0.327
Implant-related complications, n (%)	3 (27.3)	2 (25.0)	1
Unplanned reoperation, n (%)	3 (27.3)	2 (25.0)	1

APR: annual progression rate.
[a]Mean (standard deviation).
[b]Median [interquartile range].

Different distraction protocols have been suggested using either ultrasound or radiographs to measure the achieved distraction length.[10,17] Ultrasound was introduced to reduce the amount of radiation exposure from repeated radiography and shows excellent correlation with distraction length measured on radiographs.[19] However, ultrasound has a learning curve and is only able to measure the achieved distraction length. Radiographs are still performed every 6 months to monitor curve correction and implant-related complications.[17,24] Distraction protocols described so far have relied on Dimeglio's data on normal spine growth[31] and the surgeons' estimate of the desired distraction.[10,11,15,16,18,20,24,27–29] Recent studies by Lebon et al.,[16] Cheung et al.,[24] and Ahmad et al.[32] all showed that the achieved distraction length was less than that expected from the amount read on the ERC. Only one study by Hickey et al. including eight patients (four single rods and four double rods) described distraction performed "as much as the ERC would allow" within the first 6 postoperative weeks.[30] Our study is the first to describe in detail a distraction procedure relying on distraction-to-stall or "clunking" and not on estimated growth rate and ERC measurements. We performed a total of 159 distraction procedures, and 83.5% were distracted-to-stall. If the patient felt any pain or discomfort, distraction was stopped before (16.5%). In some distractions, "clunking" occurred early. Generally, we did not change the distraction interval due to early "clunking," and patients were seen at the next regular distraction. However, if early "clunking" continues in repeated distractions, increasing the distraction interval could be a solution. Also, it needs to be considered together with standing height, menarche, or other growth assessments if maximal spinal growth is achieved and the patient is ready for final surgery. This was in fact the case for one patient in our study who was 1.5 years postmenarche and Risser grade 4 by the end of the study period and planned for final fusion after three consecutive distractions with early "clunking" and unchanged standing height. Future studies of MCGR graduates will have to look into this issue.

The discrepancy between the ERC measurement and the achieved distraction length is influenced by several factors. "Cross-talking" can be a problem if rods are placed too close to each other, which might have been an issue in the six patients in our study who had two standard rods implanted at primary surgery. We now use one standard rod and one offset rod as standard construction. Distance from the skin to the actuator and resistance in the tissue can also affect the achieved distraction length.[17,33] We found no loss of distraction, and only one distraction led to persistent pain where the actuator had to be reversed in an additional procedure. The two distractions performed under general anesthesia were not related to "clunking," and subsequent distractions in these two patients were uncomplicated and performed as earlier described.

Overall, there seems to be different distraction procedures with comparable results in terms of successful distractions ("tail-gating," "set distraction amount," and "distraction-to-stall").[21,24,29,32] For comparison with other studies, we presented an annual spinal height increase; however, there are issues influencing on this measure such as PJK[10,29] and decreased lengthening of the MCGR over time.[32] Whether this decreased lengthening is related to stiffness and autofusion of the spine (the law of diminishing returns),[16,32] the construct of the MCGR[24] or a result of skeletal maturity still needs to be examined in future studies. These issues also apply to our distraction method. Distraction-to-stall can generally be done without causing

pain to the patients. The patients simply tell if they feel discomfort, and distraction is stopped or the patient is repositioned. However, one must not blindly trust "clunking," but take into account the amount read on the ERC as there is a risk of causing pain. This might have been the case in the patient experiencing pain after a distraction although the achieved distraction length after the procedure leading to pain was only 3.6 mm. The rods were distracted to clunking at the next regular interval without any complications or pain. We do not find it necessary to take full-spine radiographs more frequently than every half a year to monitor curve control, complications, and achieved distraction length, thereby reducing unnecessary radiation to these children. However, radiographs are still needed in case of a patient presenting with pain, suspected complications, or repeated early clunking before further distraction is performed.

Few studies have compared the outcomes between patients with different etiologies.[16,20] They show no difference between etiologies, but the number of patients in each category is low. We found that nonidiopathic patients had lower flexibility and a tendency toward a lower curve correction. Correspondingly, CCIs were similar in idiopathic and nonidiopathic patients, indicating that flexibility can predict the correction achieved at primary MCGR implantation.[24] There was a tendency toward a larger spinal growth and distraction length in nonidiopathic patients, which can be explained by the relative number of extra instrumented levels compared with idiopathic patients. Still, numbers in each group are increasing the risk of a type 2 error. Future large multicenter studies will have to address if equally good results can be achieved across all etiologies.

Although this was a retrospective study, we are confident in the validity of the data since patients and distraction procedures were prospectively registered. It would have been preferable to compare different distraction protocols; however, the heterogeneity and small number of patients treated with MCGR make it difficult. This is one of the largest single-center cohort studies describing a homogenous EOS population without confounding factors such as single-rod constructs or conversion cases. It is the first study to report the efficacy of a distraction-to-stall procedure, which may aid surgeons in their clinical practice as it is simple, reproducible, and efficient in increasing spinal height in EOS patients.

Conclusion

We found that MCGR effectively corrected major and secondary curve, and correction was maintained throughout the distraction period. Using a standardized distraction procedure with intended distraction-to-stall on each rod separately resulted in satisfactory spinal height increase. Implant-related complications were comparable to the available literature, and we found no difference in the outcomes between idiopathic and nonidiopathic patients.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Study approval

The study was approved by the Danish Patient Safety Authority and the Danish Data Protection Agency (journal no.: 2012-58-0004).

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Paper III

Distraction-to-stall versus targeted distraction in Magnetically Controlled Growing Rods

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Abstract

Background

Consensus is lacking regarding the lengthening procedures in magnetically controlled growing rods (MCGR), and no studies have compared the outcome between different distraction principles. The purpose of the present study was to compare distraction-to-stall with targeted distraction and identify variables associated with achieved distraction.

Methods

We performed a two-center retrospective study of all children treated with MCGR from November 2013 to January 2019, having a minimum of one-year follow-up and undergoing a minimum of three distractions. Exclusion criteria were single-rod constructs and conversion cases. In group 1 (21 patients), we used a distraction-to-stall (maximum force) principle where each rod was lengthened until the internal magnetic driver stopped ("clunking"). In group 2 (18 patients), we used a targeted distraction principle, where the desired distraction was entered the remote control before distraction. In both groups we aimed for maximal distraction and curve correction at index surgery. Achieved distraction was measured on calibrated radiographs and compared between the two groups using a linear mixed effects model (LME). Univariate and multivariate analyses were performed to identify variables associated with achieved distraction within the first year.

Results

Mean age at surgery was 9.5±2.0 years. Etiology of the deformity was congenital/structural (n=7), neuromuscular (n=9), syndromic (n=3) or idiopathic (n=20). Demographics and preoperative characteristics including spinal height (T1T12 and T1S1) did not differ significantly between the groups (p≥0.13). Time interval between distractions were mean 18 days (95% CI 10-25) shorter in group 1. Implant-related complications occurred in 10/39 patients, 5 in each group. We found no difference in achieved distraction between the groups in the LME model. In the multivariate analysis, preoperative major curve angle was the only independent variable associated with achieved distraction.

Conclusion

In two comparable and consecutive cohorts of patients treated with MCGR, we found no difference in achieved distraction between a distraction-to-stall and a targeted distraction principle. Preoperative major curve angle was the only variable associated with increased distraction.

Level of evidence: Retrospective comparative study – Level-III

Introduction

Magnetically controlled growing rods (MCGR) has become one of the preferred surgical treatments of early-onset scoliosis (EOS)[1]. The goal of the surgery is to halt progression of the deformity while allowing continuous growth of the spine. However, the technique is relatively new and despite showing advantages over traditional growing rods (TGR)[2,3], the complication and revision rate remains high[4]. Moreover, few studies have presented outcomes of patients undergoing final fusion after graduating from MCGR treatment[5,6]. There is little consensus regarding indications and timing of surgery in EOS[7]. For MCGR, there is no consensus regarding magnitude of distraction, ideal distraction length per distraction, technique and time interval between the lengthening procedures[1,8,9]. Various distraction principles have been described. The "tail-gating" principle follows published growth charts[10] with achieved distraction monitored after each distraction using ultrasound or fluoroscopy[5,11,12]. In the maximum force distraction or distraction-to-stall principle the rods are lengthened until the internal magnetic driver stops ("clunking") or the patient reports discomfort[13]. Finally, a targeted distraction can be performed based on approximated growth without monitoring achieved distraction after each lengthening. Studies of MCGR so far show a discrepancy between the achieved distraction and the amount expected from the external remote controller (ERC)[14–17]. These different distraction principles together with equipoise regarding indications and timing of surgery highlight the need for studies examining the outcome of different lengthening procedures. The purpose of this study was to compare achieved distraction between a targeted distraction and a distraction-to-stall principle. Secondly, we wanted to identify variables associated with achieved lengthening.

Materials and Methods

All patients regardless of etiology treated with MCGR at two tertiary referral centers from November 2013 through January 2019 were registered. Inclusion criteria were minimum one-year follow-up and minimum 3 distractions. Exclusion criteria were single rod constructs and conversion from other growth instrumentations. We identified 58 patients treated with MCGR in the study period; 11 patients did not fulfill the follow-up criteria, 3 had single rod constructs and 5 were conversions, leaving 39 patients for analysis. From the first center we included 21 patients (group 1)[13], and from the second center 18 patients (group 2). Patients were followed throughout the study period or until definitive fusion surgery.

Both centers used the same operative technique with dual rod constructs in accordance with international recommendations[1,9]. Maximal curve correction and distraction were intended intraoperatively during insertion of the rods. The rods were contoured, and the actuator tested manually before insertion. Anchor point fixations were performed with pedicle screws, where applicable, and/or otherwise hooks. Additional hooks and cross-links were added at the discretion of the surgeon.

The lengthening procedures were generally performed in the outpatient clinic with the patient lying on the side or in a prone position. Distractions were performed on each rod separately. In group 1 we used a maximum force or distraction-to-stall principle; in group 2 we used a targeted distraction principle. For both groups, curve correction, implant failure and achieved distraction were monitored with radiographs every 6 months.

Data

From a chart review we collected baseline characteristics including primary diagnosis, information about the surgery and lengthening procedures. Etiology was defined according to

the Classification of Early-Onset Scoliosis (C-EOS)[18]. Complications were defined as infection- or implant-related[19]. Spinal height (T1S1), thoracic height (T1T12) and achieved distraction on both rods were measured at each radiographic assessment by the primary author according to international standards[20]. Achieved distraction was reported as the mean of measurements between the two rods. Total achieved distraction within the first year was calculated for each patient. All images were calibrated with the diameter of the actuator to account for magnification error. Radiographs were uploaded to the validated online imaging software KEOPS (SMAIO, Lyon, France)[21] where major curve angle and global kyphosis was measured. T1T12 and T1S1 were measured pre- and postoperatively, at one- and two-year follow-up.

The study was approved by the local institutional review board (BCM H-43238), local health authorities (j.nr: 3-3013-1911/1/) and data protection agency (j.nr.: 2012-58-0004).

Statistics

Statistical analyses were performed using R, version 3.5.3. Data were assessed with histograms, scatter plots and quantile-quantile plots and presented as proportions (%), means ± standard deviation or medians with inter quartile range. Repeated measures of spinal height and achieved distraction were visualized in linear

Table 1. Demographic data and comparison of baseline variables between the groups.

	Group 1 (n=21) Distraction-to-stall	**Group 2 (n=18) Targeted distraction**	**p-value**
Age at index surgery, years	9.6 (1.8)	9.4 (2.3)	0.781
Sex (female), n (%)	10 (47.6)	11 (61.1)	0.523
Etiology, n (%)			0.465
Congenital/structural	4 (19.0)	3 (16.7)	
Idiopathic	9 (42.9)	11 (61.1)	
Neuromuscular	5 (23.8)	4 (22.2)	
Syndrome	3 (14.3)	0 (0.0)	
Preoperative major curve angle, °	73 (18.1)	82 (18.7)	0.138
Preoperative global kyphosis, °	45.2 (21.7)	42.3 (20.9)	0.687
Curve correction, %	39.5 (15.5)	34.9 (11.5)	0.302
Mechanical complication, n (%)	5 (23.8)	5 (27.8)	1
Medical complication, n (%)	2 (9.5)	1 (5.6)	1
Unplanned reoperation, n (%)	5 (23.8)	4 (22.2)	1
Time interval between lengthening, days	78.5 (27.2)	96.2 (35.5)	**<0.001**
Instrumentation length, n. median [range]	12 [11- 17]	12 [10- 17]	0.293
Rod diameter			**0.011**
4.5 mm	5 (23.8)	12 (66.7)	
5.5 mm	16 (76.2)	6 (33.3)	
Preoperative T1T12, mm	182.6 (31.8)	175.4 (34.4)	0.509
Preoperative T1S1, mm	296.1 (48.3)	294.1 (50)	0.899
Postoperative T1T12, mm	203.7 (29.9)	198.3 (26)	0.547
Postoperative T1S1, mm	334.1 (42.9)	326.2 (41.1)	0.560

Data are presented as means (standard deviation) unless otherwise specified.

Table 2. Measures of major curve angle, global kyphosis, T1T12 and T1S1 for both groups.

	Preoperative (n = 39)	Postoperative (n = 39)	1-year follow-up (n = 39)	2-year follow-up (n = 27)
Major curve angle, °	77 (19)	49 (18)	51 (16)	51 (14)
Global kyphosis, °	44 (21)	32 (15)	42 (19)	39 (14)
T1T12, mm	179 (33)	201 (28)	212 (29)	226 (26)
T1S1, mm	295 (49)	330 (42)	343 (42)	364 (39)

Data are presented as means (standard deviation)

plots. Categorical data were compared using Fisher's exact test and continuous data with student's t-test or Wilcoxon rank sum test.

Achieved distraction over time was compared between the two groups with a fitted linear mixed effects model adjusting repeated measures for number of instrumented levels. Univariable analyses were performed to identify variables associated with achieved distraction within the first year. The variables included in the analyses were predetermined based on parameters previously reported in the literature[5,6,8,14–16,22–26]. A multiple linear regression was performed to control for any potential confounding including variables significantly associated with achieved distraction in the univariate analysis ($p < 0.05$). The model was checked for interactions.

Results

We included 39 patients treated with MCGR with a mean age at primary surgery of 9.5±2.0 years. Mean follow-up to most recent distraction or definitive surgery was 28.1±10.9 months with an average 11.2 months longer follow-up in group 1 ($p<0.001$). All patients completed 1-year follow-up. One patient continued treatment at another hospital after one year and was lost to follow-up, and two patients underwent definitive surgery within 2 years from primary surgery. Furthermore, nine patients did not reach 2-year follow-up within the study period resulting in 27 patients for radiographic assessment at 2-year follow-up. Etiology was congenital/structural in 7, neuromuscular in 9, syndromic in 3 and idiopathic in 20 patients, with no difference in distribution between the two groups (Table 1). There was no difference between the groups regarding preoperative major curve angle and kyphosis, curve correction, instrumentation length or preoperative T1T12 or T1S1 (Table 1). However, the mean time interval between lengthening was 18 days [95%CI 10-25] longer in group 2 compared with group 1. Complications were screw loosening (n=5), hook/rod dislodgement (n=2) and rod breakage (n=3). All rod breakages occurred with 4.5 mm rods. Medical complications were aspiration pneumonia (n=1), superficial wound infection (n=1) and deep infection (n=1). We found no difference in complication or unplanned reoperation rates between the groups (Table 1).

For both groups, the major curve angle was reduced postoperatively with mean 29° [95% CI 25-32] (Table 2), and correction was maintained at 1-year and 2-year follow-up ($p<0.001$) (Figure 1a). Similarly, global kyphosis was reduced postoperatively with mean 13° [95%CI 8-18] (Table 2); however, this reduction was not maintained at 1-year and 2-year follow-up ($p>0.168$) (Figure 1b). We found no difference between the groups at follow-up regarding major curve angle, global kyphosis, T1T12 and T1S1 (Figure 2).

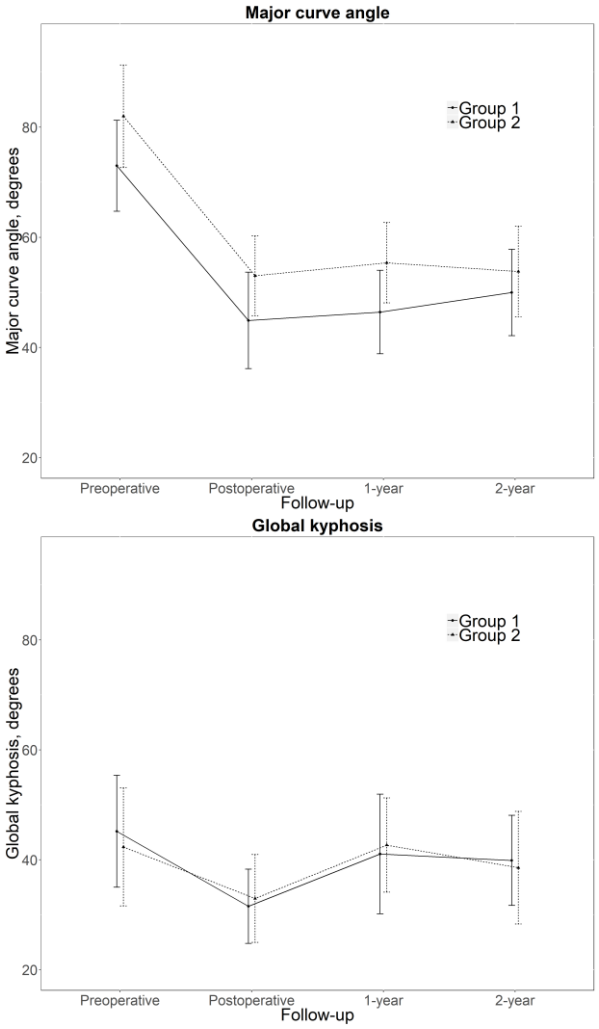

Figure 1a and 1b. Follow-up of major curve angle and global kyphosis in the two groups. Reported as means with error bars representing 95% confidence intervals of the mean.

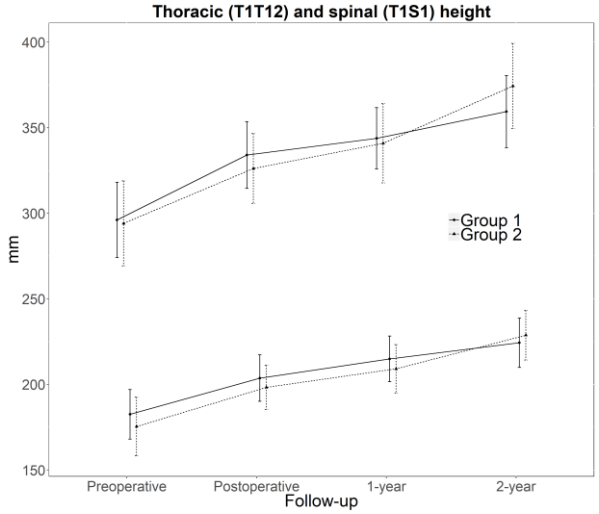

Figure 2. Follow-up of thoracic height T1T12 (bottom) and spinal height T1S1 (top) in the two groups. Reported as means with error bars representing 95% confidence intervals of the mean.

In the linear mixed effects model, we found no difference in achieved distraction between the two groups (p = 0.521) (Figure 3). Also, we found no difference in achieved distraction on the concave rod (p = 0.202) or the convex rod (p= 0.916). Mean achieved distraction within 1 year for both groups were 12.7±6.2 mm (range 2.6-25.6), not adjusted for instrumentation length. Results from the univariate analysis are presented in Table 3. Preoperative major curve angle, instrumentation length and preoperative T1T12 and T1S1 were the only variables significantly associated with achieved distraction within 1 year. As T1T12 and T1S1 measures are strongly correlated, we chose to only include T1T12 in the multivariate model. Preoperative major curve angle was the only independent variable associated with achieved distraction (Table 4).

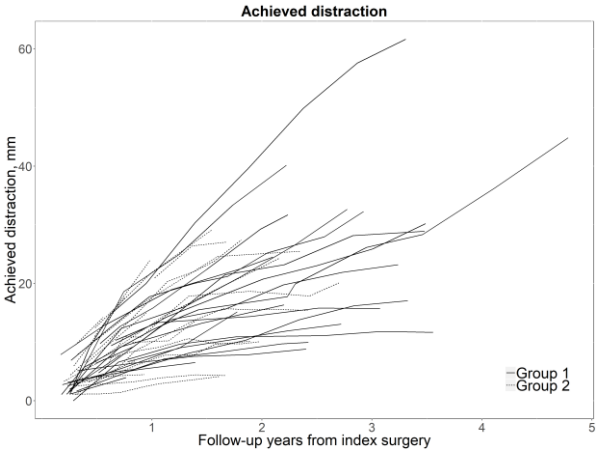

Figure 3. Linear plot of achieved distraction (mean of concave and convex rod) between the two centers. Each line represents the distraction in the individual patient.

Table 3. Univariate analysis of variables associated with achieved distraction within the first year after index surgery.

Variable	Estimate, mm/year [95% confidence interval]	p-value
Age at index surgery, years	-0.4 [-1.4; 0.6]	0.421
Etiology*	-	0.066
Instrumentation length, n	1.5 [0.5; 2.4]	0.003**
Location of major curve, thoracic vs. lumbar*	-	0.289
Preoperative T1T12, cm	-0.7 [-1.3; -0.2]	0.015**
Preoperative T1S1, cm	-0.5 [-0.9 -0.1]	0.010**
Preoperative major curve, °	0.17 [0.08; 0.27]	<0.001**
Preoperative global kyphosis, °	0.04 [-0.06; 0.13]	0.462
Correction index, %	-0.07 [-0.22; 0.08]	0.341
Time interval between lengthening, weeks	0.31 [-0.42; 1.04]	0.401

*Non-parametric test - estimates not applicable.
**Significance level <0.05

Discussion

In this retrospective study of two consecutive and comparable cohorts of patients treated with MCGR, we found no significant difference in achieved distraction between a distraction-to-stall and a targeted distraction principle. In a multivariate analysis, the only independent variable associated with achieved distraction was preoperative major curve angle.

Increased focus has been raised towards lengthening procedures in MCGR[8,15,27]. Corresponding to our findings, MCGR has been shown to correct the coronal deformity and maintain this correction throughout the treatment[3,5,6,14,16,23,24,26,28].

Concurrently, the thoracic and spinal height (T1T12 and T1S1) in this study increased throughout treatment. However, changes in the sagittal profile such as proximal junctional kyphosis (PJK) or adding on deformity can alter measurements of thoracic and spinal height, hence, they become unreliable as an outcome of successful distractions (Figure 4). Achieved distraction was therefore chosen as the primary outcome, and the mean 12.7mm/year reported in this study corresponds to the normal thoracic height gain during the growth spurt of 1.1 mm/year as reported by Dimeglio & Canavese[10].

The primary purpose of this study was to compare two different distraction principles. We have previously described the distraction-to-stall principle used in group 1[13]. The targeted distraction used in group 2 resembles the tail-gating principle by trying to predict spinal growth and follow this with distractions. We found no difference between these distraction principles in this study, despite a difference in time interval

Table 4. Multivariate analysis of variables significantly associated with achieved distraction within the first year after index surgery.

Variable	Estimate, mm/year [95% confidence interval]	p-value
Preoperative major curve, °	0.15 [0.03; 0.26]	**0.012**
Instrumentation length, n	1.04 [-0.03; 2.10]	0.056
Preoperative T1T12, cm	0.11 [-0.61; 0.83]	0.753
R^2 for the model was 0.361		

between lengthening procedures between the groups. The question is whether the principles are equivalent. In maximum force distraction, the procedure is stopped when the resistance against further distraction exceeds the power transferred to the internal magnetic driver ("clunking"), and thus clunking should not be considered a failure of distraction. Achieved distraction still needs to be assessed with radiographs every 6 months along with monitoring for complications. Early clunking can together with no achieved distraction over several lengthening procedures indicate failure of the rod to distract. Clunking also occurred during the targeted distraction procedures, but the frequency of clunking was not consistently reported for patients in group 2 and any differences between the groups could therefore not be assessed. With the targeted distraction technique, one must account for the discrepancy between expected distraction (the amount set on the ERC) and the achieved distraction[14–17,29]. Factors such as BMI, distance to and between the actuators has been suggested to be the cause[14,15,17], and over time the relationship between achieved and expected distraction might decrease to 1/3[17]. Moreover, an in vitro study showed that the force generated by the implant itself decreased with the distracted length[30]. These multiple factors illustrate the difficulties in predicting achieved distraction and suggest that lengthening is closely monitored fluoroscopically or with ultrasound[5,6]. Nevertheless, we found no difference in achieved distraction over time between the distraction techniques in this study. It is likely that clunking will occur in targeted distraction when the amount set on the ERC is larger than the rod's capability to distract due to the abovementioned factors. In this case the two distraction techniques are equivalent. We encourage future studies to describe the lengthening procedure and the frequency of clunking in more detail.

Former studies of MCGR have shown a wide range in achieved distraction between individuals[5,6,26]. The only independent

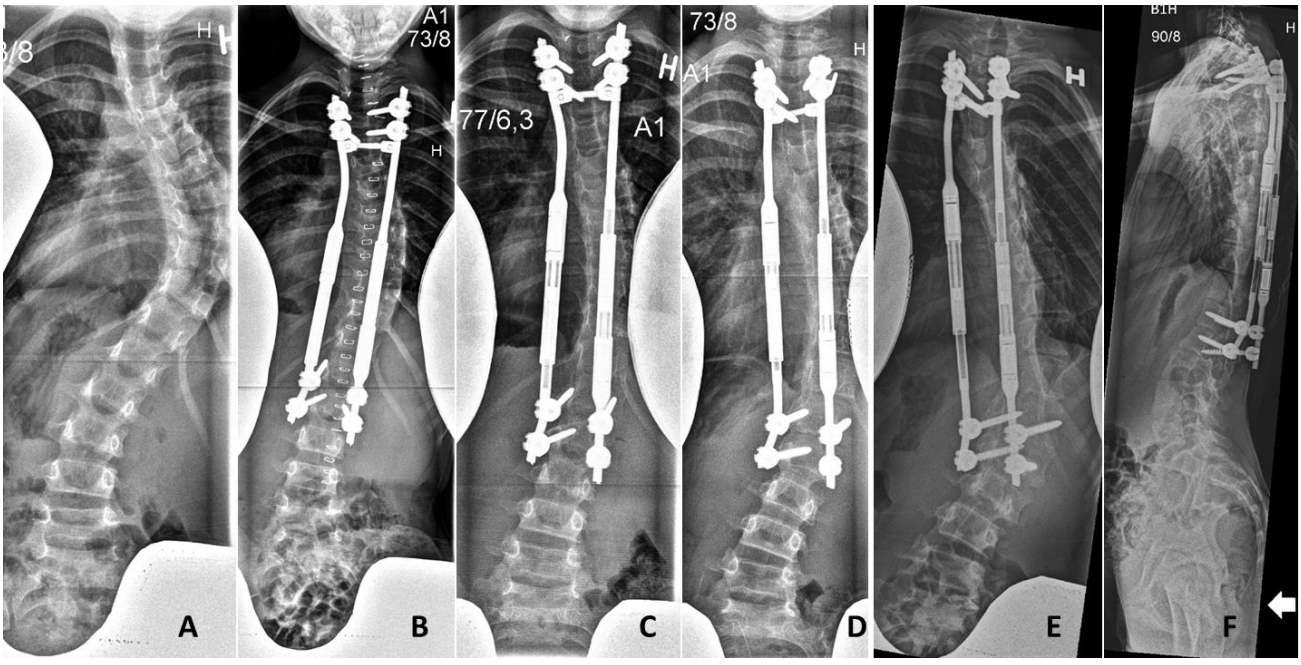

Figure 4. The very first patient operated in our cohort, 8 years old. This patient had a juvenile idiopathic scoliosis with a preoperative major curve angle of 77°. Radiographs shown are preoperative (A), postoperative (B), at 1.5-year (C), 3-year (D) and 4.5-year postoperatively, antero-posterior (E) and lateral (F). Postoperatively, major curve was reduced to 41°. After 1.5 years she developed pain at the distal anchor site. A CT-scan showed screw loosening and she was re-operated with exchange of both rods. She had undergone 27 distractions at latest

predictor of achieved distraction was preoperative major curve. The two groups in the study were comparable apart from a longer time interval between lengthening in group 2. However, we found no association between the time interval and achieved distraction. Distraction interval is the focus of a planned randomized controlled trial[8]; however, other factors such as burden of care, travel distance to the hospital and an individualized approach to each patient might also influence on the decided lengthening interval. A 1-year achieved distraction outcome was chosen due to some patients in our cohort undergoing definitive fusion surgery with 2 years from index surgery. From the linear plots of achieved distraction over time (Figure 3), distraction within the first year seemed to predict achieved distraction throughout follow-up with no sudden increase or decline in the slope for individual patients. The multivariate analysis showed an expected but not statistically significant tendency towards larger achieved distraction with the length of instrumentation. We suggest this variable should be included in the calculation of expected distraction and adjusted for in comparison between individuals[8]. Preoperative T1T12 and T1S1 were inversely correlated with preoperative major curve which is probably why they had no effect in the multivariate analysis. The association between preoperative major curve and achieved distraction suggests that additional curve correction is achieved during lengthening procedures. However, judged from the R2, there is still a large variation between individuals to be explained.

A high complication rate remains an unsolved problem in the MCGR treatment. Concerns has been raised that maximum correction during implantation of the rods might stress the implants and cause complications. However, a large proportion of spinal height increase is achieved at primary surgery and substantial curve correction beyond that achieved at implantation cannot be expected[5]. The mechanical complication and unplanned reoperation rates in this study are lower than reported in a recently published review by Thakar et al. (44.5% and 33% respectively)[4]. All rod breakages in our cohort occurred in 4.5 mm rods outside the housing unit. However, absolute numbers of complications are still small, and the difference in follow-up time and number of patients with 4.5 mm rods between the two groups make it difficult to draw any conclusions.

This is the first study to compare the outcome between distraction techniques in MCGR. Inherently, cohort studies of MCGR include relatively small number of patients with the risk of making false conclusions due to type 2 errors. However, this is one of the largest series of MCGR treated patients and we took caution not to include too many variables in the models. The indications and timing of surgery is still debated[7–9]. We only included age, thoracic and spinal height as variables representing growth stage. Risser grade could not be validly judged due to radiation sparring protection on radiographs (Figure 4). To improve knowledge on patient selection, we encourage future studies to systematically include objective growth assessment other than age prior to surgery. A substantial remaining growth potential is imperative for justifying the MCGR procedure.

In conclusion, we found no difference in achieved distraction between a distraction-to-stall and a targeted distraction principle. The groups were comparable apart from a difference in time interval between the lengthening procedures, however, we found no association between the distraction interval and achieved distraction. The only variable independently associated with increased distraction was preoperative major curve angle.

Acknowledgements

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Paper IV

Does magnetically controlled growing rods lead to low bone mineral density in instrumented vertebrae? – a feasibility study.

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Abstract

Study design

Cross-sectional feasibility study.

Objectives

To investigate the feasibility of measuring bone mineral density (BMD) in vertebrae within the instrumentation of patients treated with magnetically controlled growing rods (MCGR). Secondly, to compare BMD to vertebrae below the instrumentation and total hip. And finally, to explore associations with time from MCGR index surgery.

Summary of background data

Studies show morphometric changes of vertebrae in the treatment with distraction-based growth instrumentation. However, no studies have examined the bone quality of vertebrae within the instrumentation with dual-energy X-ray absorptiometry (DXA).

Methods

We conducted a cross-sectional study of BMD in patients treated with MCGR at our institution. Exclusion criteria were structural deformities at the vertebrae of interest, conversion cases, inability to stand and walk or patients who had undergone definitive spinal fusion. Eleven patients fulfilled the study criteria and underwent DXA scans during 2018. We measured areal BMD (aBMD, g/cm2) of both hips and in the spine using a software to exclude high density pixels from implant metal. aBMD was measured on the 3 vertebrae within the instrumentation above the lower anchor point and the 3 vertebrae below the instrumentation. We calculated individual age-adjusted aBMD Z-scores ($aBMD_{age}$ Z-score) and height-for-age adjusted aBMD Z-scores ($aBMD_{HAZ}$) from a reference population, and relative aBMD of the instrumented vertebrae by dividing with total hip aBMD. Associations between relative aBMD and $aBMD_{HAZ}$ Z-score, respectively, and time from MCGR index surgery were assessed. Results are reported with medians and inter-quartile range [iqr].

Results

Age at examination was 13.5 [10.0-14.4] years. $aBMD_{HAZ}$ Z-score for total hip was 0.9 [0.6, 1.2] and for vertebrae within the instrumentation -2.5 [-3.1, -1.9]. We found a statistically significant lower aBMD in the vertebrae within the instrumentation ($p = 0.002$) and vertebrae below the instrumentation ($p = 0.031$) compared with total hip aBMD. We found a lower but not statistically significant aBMD for vertebrae within the instrumentation compared with vertebrae below the instrumentation ($p = 0.063$). We found no associations between time from MCGR index surgery and relative aBMD or $aBMD_{HAZ}$ Z-score for instrumented vertebrae.

Conclusions
Measuring BMD of the instrumented vertebrae is feasible; however, it comes with several limitations. We found a lower aBMD of vertebrae within the instrumentation compared with total hip aBMD but no association with time from MCGR index surgery.
Level of evidence
Level IV – case series

Key points
- Measuring areal bone mineral density (aBMD) of the instrumented vertebrae in patients treated with magnetically controlled growing rods (MCGR) is feasible.
- We found statistically significant lower aBMD of vertebrae within the instrumentation compared with total hip aBMD. aBMD was also lower compared with vertebrae below the instrumentation, but not statistically significant.
- There was no association between relative aBMD of instrumented vertebrae and time from MCGR surgery.
- The results require validation in a longitudinal study design.

Introduction
Magnetically controlled growing rods (MCGR) is a distraction-based surgical treatment for skeletally immature patients with early-onset scoliosis (EOS). MCGR efficiently controls curve progression while allowing continuous growth of the spine. However, the treatment has a high complication rate (44.5%)[1] and long-term results after definitive spinal fusion are sparse[2,3]. Moreover, the impact of distraction-based techniques on the vertebral bone formation and quality is unknown. Bone quality is primarily quantified with bone mineral density (BMD) and the golden standard for examining BMD is dual energy X-ray absorptiometry (DXA)[4]. In patients with adolescent idiopathic scoliosis (AIS), a low BMD (Z-score < -1) has been found in 27-36% of patients and may be associated with progression of the scoliosis[5–8]. However, no studies have examined BMD in patients with EOS. A few studies have reported morphometric changes of the vertebral bodies within the instrumentation compared with vertebral bodies outside the instrumentation in traditional growing rods (TGR) and Vertical Expandable Prosthetic Titanium Rib (VEPTR®), respectively[9–11]. Whether this change is caused by stress-shielding of the vertebrae or distractive forces applied to the growth plates is unknown. We hypothesized that stress-shielding of the vertebrae within the instrumentation of the MCGR results in lower bone quality quantified by BMD measurements.
The purpose of this study was to investigate the feasibility of measuring BMD in the vertebrae within the MCGR instrumented levels. Secondly, to compare this to BMD of the hip and the vertebrae outside the instrumentation. And finally, to explore a possible relationship between BMD within the instrumentation and time from MCGR implantation.

Materials and Methods
We conducted a cross-sectional study of patients treated with MCGR at our institution. Exclusion criteria were structural deformities at the vertebrae of interest, conversion cases and inability to stand and walk. All patients had undergone index surgery in the period November 2013 to April 2018, and the BMD measurements were carried out from April through September 2018. At the end of the study period, a total of 25 patients had undergone surgery with MCGR. Two were conversion cases, 3 underwent definitive spinal fusion before initiation of the study, 2 had structural deformities, 5 had no standing/walking function, and 2 children could not cooperate to the examination leaving 11 patients to be scanned. Patients were scanned either at a MCGR lengthening visit or prior to a planned definitive spinal fusion.

Measurements of BMD (g/cm2) were performed with a Norland XR-46 bone densitometer (Norland Corp, Fort Atkinson, WI) according to the International Society for Clinical Densitometry guidelines[12]. The setup and positioning of the patient were similar to measuring BMD in the lumbar spine (Figure 1).

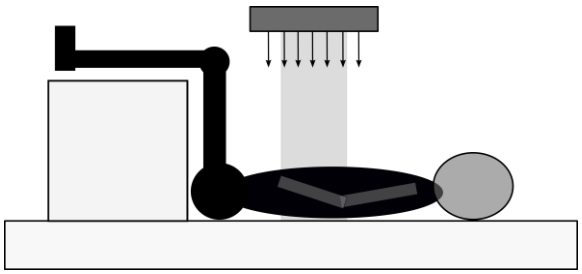

Figure 1. The setup and positioning of the patient when measuring bone mineral density of the spine.

We used a software customized to exclude high density pixels from implant metal, allowing measurement to be performed close to the MCGR. The technique has been described in evaluation of BMD around hip and knee prostheses[13] and previously used to assess BMD in the scoliotic spine[5]. We measured areal bone mineral density (aBMD) in the 3 vertebrae above the lower anchor point within the instrumentation (zone a1-a3), at the anchor point (zone i0) and in the 3 vertebrae below the instrumentation (zone b1-b3), (Figure 2). These zones were drawn manually in the scanner software by the primary author. Areal BMD values were measured in both hips to account for potential side differences in scoliotic patients[5,14] and reported as mean between right and left aBMD. Areal BMD values within and below the instrumented levels were reported as the mean of the 3 measured vertebrae, a1-a3 and b1-b3 respectively. Measurements of aBMD in vertebrae below the instrumentation could not be obtained in 5 patients due to instrumentation of lumbar vertebrae or an insufficient scan area.

Individual age-adjusted Z-scores for height and body mass index (BMI) were calculated from a national reference population[15]. Using the reference population from "The Bone Mineral in Childhood Study", we calculated individual age-adjusted aBMD Z-scores ($aBMD_{age}$ Z-score) and height-for-age adjusted aBMD Z-scores ($aBMD_{HAZ}$ Z-score)[16,17]. To explore associations between time from implantation of MCGR and aBMD of the spine, we calculated a relative aBMD of the vertebra within instrumentation by dividing with total hip aBMD. Relative aBMD and $aBMD_{HAZ}$ Z-score were plotted against time from MCGR index surgery.

The study was approved by the regional committee on health research ethics (j.no.: H-18010812) and the data protection agency (j.nr.: 2012-58-0004). Written informed consent was retrieved from both parents/legal guardians and, if above 15 years old, also from the child.

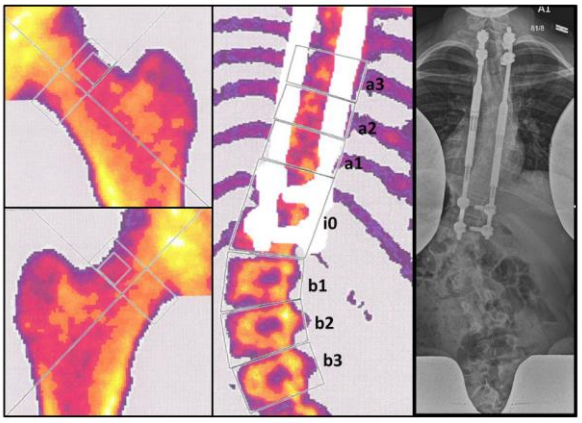

Figure 2. Areal bone mineral density (aBMD) measurements prior to spinal fusion surgery in a 14-year-old girl diagnosed with juvenile idiopathic scoliosis and treated with magnetically controlled growing rods. To the left: aBMD of left and right total hip; Middle: aBMD of the spine with the zones of interest. Mean aBMD of vertebrae within the instrumentation (zone a1-3) was 0.676 g/cm^2 and aBMD of vertebrae below the instrumentation (zone b1-3) was 0.795 g/cm^2; To the right: Anterior-posterior radiograph at the time om examination showing a major curve of 40 degrees.

Statistics

Statistical analyses were performed using R, version 3.5.3. Data were assessed with histograms and quantile-quantile plots and presented as proportions (%) or medians with interquartile range. Measurements of aBMD and

corresponding Z-scores were compared with Wilcoxon signed rank test. Linear regressions were performed to test associations between time from MCGR index surgery and relative aBMD and $aBMD_{HAZ}$ Z-scores respectively.

Table 1. Demographic data.	
Age at index surgery, years	10 [7.7, 11.8]
Sex (female), n (%)	7 (63.6)
Etiology, n (%)	
Congenital	2 (18.2)
Idiopathic	7 (63.6)
Syndrome	2 (18.2)
Preoperative major curve angle, °	64 [56, 78]
Preoperative global kyphosis, °	45 [31, 54]
Curve correction, %	43.8 [37.7, 47.7]
Upper instrumented vertebra, n (%)	
Th2	6 (54.5)
Th3	5 (45.5)
Lower instrumented vertebra, n (%)	
Th12	1 (9.1)
L1	4 (36.4)
L2	4 (36.4)
L3	1 (9.1)
L4	1 (9.1)
Results are presented as medians with inter quartile range [iqr] unless otherwise specified.	

Results

Eleven patients underwent DXA scanning of both hips and the spine. Patient characteristics are summarized in Table 1. Two patients had Marfan syndrome, one had Neurofibromatosis type 1 and one had scoliosis following congenital diaphragmatic herniation operated in infancy. The etiology for the remaining patients was idiopathic. All patients were physically able to participate in school gymnastics, but none of them performed high impact sports on a regular basis. Patients were scanned median 33 months from index surgery (range 5-57 months). Anthropometrics and measurements of aBMD and corresponding Z-scores are reported in Table 2. We found a statistically significant lower aBMD in the vertebrae within instrumentation ($p = 0.002$) and vertebrae below the instrumentation ($p = 0.031$) compared with total hip aBMD. We found a lower but not statistically significant aBMD for vertebrae within the instrumentation compared with vertebrae below the instrumentation ($p = 0.063$), (Figure 3). Equal results were achieved by comparing $aBMD_{age}$ and $aBMD_{HAZ}$ Z-scores between vertebrae within the instrumentation, vertebrae below the instrumentation and total hip, respectively. In the linear regression analyses, we found no associations between time from MCGR index surgery and relative aBMD (Figure 4a) or $aBMD_{HAZ}$ Z-score (Figure 4b) for vertebrae within the instrumentation.

Discussion

In this feasibility study, we explored bone quality of the vertebrae within the instrumentation in patients treated with MCGR. Areal BMD of vertebrae below the instrumentation was significantly lower than total hip aBMD but also lower than age-matched controls. Moreover, we found a trend towards lower aBMD in vertebrae within the instrumentation compared with vertebrae below the instrumentation. We could not detect any association between time from MCGR index surgery and aBMD of the vertebrae within the instrumentation.

Reduced bone quality is associated with increased complication rates in adult spinal deformity surgery[18,19], but whether this applies to pediatric spinal deformity is unknown. BMD in childhood strongly determines the BMD through adolescence, and it is decisive for peak bone mass and fracture risk later in life[20]. A recent study by Watanabe et al. showed long-term persistent vertebral osteopenia after posterior fusion in AIS caused by stress-shielding of the instrumented vertebrae[21]. Moreover,

Table 2. Demographics at examination and measurements of areal bone mineral density (aBMD)			
Variable	**Median [iqr]**	**Z-score for age**	**Height-for-age adjusted Z-score**
Age, years at examination	13.5 [10.0, 14.4]	-	-
Height, cm	149 [142, 160]	-0.9 [-1.7, 1.3]	-
Weight, kg	33.7 [29.4, 51.5]	-	-
Body mass index (BMI), kg/m^2	17.0 [14.6, 18.8]	-0.7 [-1.7, 0.6]	-
Time from index surgery, months	33 [22, 36]	-	-
Major curve angle at examination, °	52 [41, 62]	-	-
aBMD femoral neck, g/cm^2	0.790 [0.702, 0.833]	0.1 [-0.5, 1.2]	0.2 [-0.1, 0.3]
aBMD total hip, g/cm^2	0.929 [0.818, 1.004]	0.7 [0.0, 1.4]	0.9 [0.6, 1.2]
aBMD within instrumentation, g/cm^2	0.517 [0.456, 0.635]	-2.4 [-3.6, -2.0] *	-2.5 [-3.1, -1.9] *
aBMD at lower anchor point, g/cm^2	0.679 [0.561, 0.771]	0.9 [-1.5, 0.4] *	-1.0 [-1.3, 0.2] *
aBMD below instrumentation**, g/cm^2	0.697 [0.591, 0.779]	-1.2 [-1.8, -0.7]	-1.0 [-1.9, -0.3]
Results are presented as medians with inter quartile range [iqr]. aBMD: areal Bone Mineral Density. *Lumbar spine aBMD was chosen as a reference for calculating Z-scores, **Results from 6 patients			

vertebral osteopenia was independent of implant removal. These results support that the lower vertebral age-adjusted aBMD found in this study will persist through adolescence and adulthood.

Areal BMD measurements in deformed vertebrae should be interpreted with some precautions. The three vertebrae within the instrumented levels were chosen to minimize influence of ribs and sternum. Moreover, they were presumably the least deformed instrumented vertebrae and not part of the major curve apex which typically involves the most deformed and rotated vertebrae. Hence, they provided the most reliable measurements of aBMD[4]. Total body or lumbar spine BMD are the preferred measurements of BMD in pediatric DXA[12]; however, these could not be assessed due to influence of the MCGR implant. Therefore, the mean of right and left total hip aBMD were chosen to represent the general BMD in the patients. Areal BMD in total hip and lumbar spine in the current study were comparable to the background population[17].

Whether a lower aBMD of the instrumented spine as found in this study is inherent to the scoliotic spine or a result of the distraction needs further examination[22]. Measurements of aBMD in the thoracic and lumbar spine are comparable in an adult normal population[23], and BMD assessed with High Resolution quantitative Computed Tomography (HRqCT) is possibly even higher in the lower thoracic vertebrae compared with the lumbar[24]. These results emphasize our findings of a tendency towards lower aBMD in the instrumented vertebrae compared with vertebrae below the instrumentation as a possible result of the MCGR instrumentation.

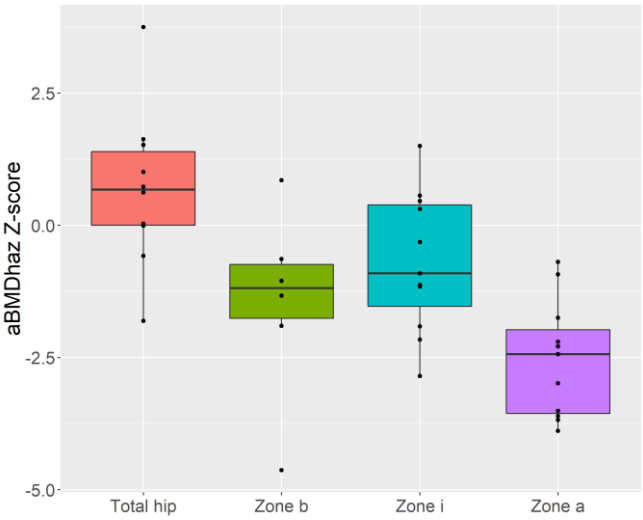

Figure 3. Boxplot of height-for-age adjusted areal bone mineral density ($aBMD_{HAZ}$) Z-score for total hip (mean between right and left), vertebrae below the instrumentation (Zone b), vertebra at lower anchor site (Zone i) and instrumented vertebrae (Zone a). According to international guidelines a Z-score of <-2 is defined as low bone mineral density[101].

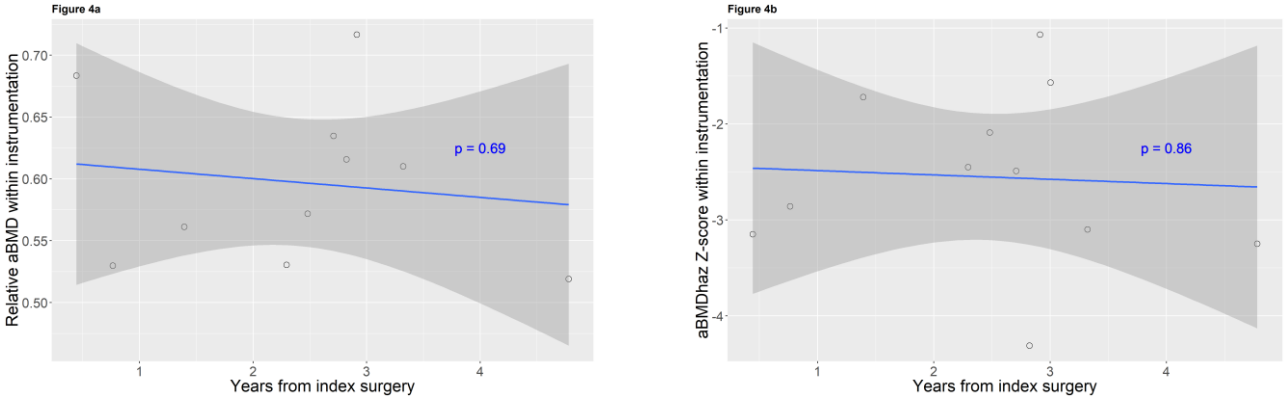

Figure 4a and 4b. Relative areal bone mineral density (relative aBMD) (Figure 4a) and height-for-age adjusted aBMD ($aBMD_{HAZ}$) Z-score (Figure 4b) plotted against time from index surgery. Relative aBMD was calculated as aBMD of instrumented vertebrae divided by total hip aBMD. Linear regression lines and corresponding p-value for the linear models are shown (blue).

However, this is still a hypothesis that requires confirmation in a longitudinal setup.

Studying and understanding the consequences of MCGR implantation on vertebral growth, morphometrics and bone quality might help lower complication rates. Studies have shown relative increases in vertebral body height within the instrumentation compared with vertebrae outside the instrumentation using TGR and VEPTR respectively[9–11]. Similar to MCGR, these principles rely on distraction-based techniques and the results regarding bone morphology are most likely applicable to patients treated with MCGR. These morphometric changes might explain a relative loss of aBMD in the vertebra within the MCGR. However, whether the changes in shape is caused by stimulation of the growth plates due to distractive forces[9] or a result of stress-shielding with reduced axial loading[11] is unknown. Theoretically, the changes in vertebral morphology and bone quality would be more pronounced with longer time from index surgery; however, our results could not support this hypothesis.

This study has several limitations. Due to the cross-sectional design, we cannot draw any conclusions on the causality between a low spinal BMD and the MCGR treatment. Moreover, we compared our results to a background population with BMD measured on different DXA scanners[17]. However, results from this background population were comparable to other reference populations and we measured total hip to make patients their own controls. Measuring aBMD in a scoliotic spine partly covered by metal implants is challenging and more valid measures might be achieved with HRqCT. However, this would require repetitive large radiation doses to an already exposed pediatric population which cannot be justified. Finally, the heterogeneity and small number of patients increase the risk of a type 2 error, but this is inherent to most studies of EOS patients. To the best of our knowledge, this is the first study assessing bone quality in patients treated with MCGR and it provides a base for future studies in this field.

Conclusion

Measuring BMD of the spine is feasible in MCGR patients. However, it comes with several limitations, and the results in this study need to be confirmed in a longitudinal study design. Nevertheless, we found evidence supporting our hypothesis that MCGR results in lower aBMD of vertebrae within the instrumentation. We did not find any association between aBMD of vertebrae within the instrumentation and time from MCGR index surgery.

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