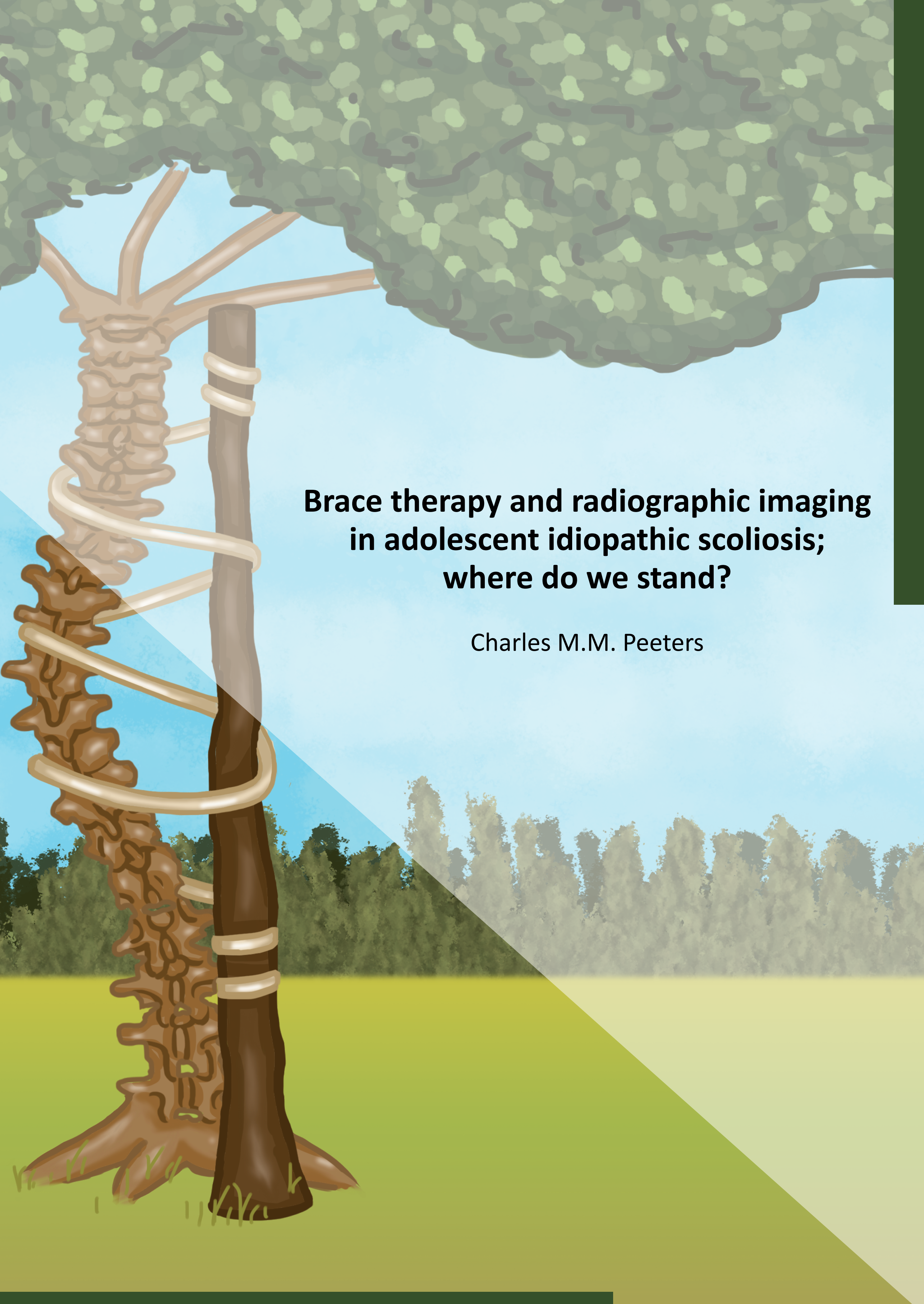

Brace therapy and radiographic imaging in adolescent idiopathic scoliosis; where do we stand?

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CHAPTER 1

General introduction, aims, and outline of this thesis

INTRODUCTION

Idiopathic scoliosis

Idiopathic scoliosis is a complex three-dimensional (3D) deformity of the spine. The term scoliosis comes from the Greek word 'skoliosis' which means crooked, and the term 'idiopathic' applies to all patients without a known underlying disease causing the deformity[1, 2]. Idiopathic scoliosis is by far the most common type of scoliosis (approximately 80% of the cases) with a prevalence of 1-3% in the general population[2, 3]. In children, it can be subdivided in early onset and late onset idiopathic scoliosis, or in infantile, juvenile and adolescent idiopathic scoliosis (AIS)[1]. Most patients with idiopathic scoliosis (89%) typically present after 10 years of age during the adolescent growth spurt and are therefore classified as AIS[3].

The diagnosis of idiopathic scoliosis is confirmed when there is a lateral curvature of 10 degrees or higher on the coronal plane of a radiograph and axial rotation can be recognized[2]. In general, the curvature can be high thoracic, main thoracic or thoracolumbar/lumbar, but the deformity is much more complex than that. Besides deviations in the coronal plane and axial rotation, idiopathic scoliosis can also be characterized by alterations in the sagittal plane such as hypokyphosis, pedicle asymmetry, asymmetrical closure of the neurocentral cartilages, hypertrophy of the facet joints, rib cage deformity, spine-airway proximity, bronchial narrowing, and lung function loss[1, 4-7].
Interestingly, idiopathic scoliosis is believed to occur exclusively in humans[8, 9]. A scoliosis is found rarely in other vertebrates, and is in those cases usually caused by anatomic abnormalities[9]. The unique upright biomechanics of the upright human spine, with significantly decreased rotational stability, has been shown to play an important role in the initiation of the scoliosis[8, 9]. However, the exact etiology and pathogenesis of idiopathic scoliosis has still not been elucidated, and a multifactorial origin can be assumed[1, 2, 8].

Adolescent idiopathic scoliosis develops during childhood and progresses severely in 0.1-0.3% of the diagnosed adolescents[10]. Curve progression is much more common in females. High spinal growth velocity during early pubertal growth spurt is an important predisposing factor for a rapid increase of the deformity[2, 10-13]. When untreated, severe scoliosis may lead to severe trunk deformities with both restrictive and obstructive lung disease, pain, decreased health-related quality of life (HRQOL), cosmetic issues, and progressive functional limitations[2, 7, 10]. For this reason, the basic goals of scoliosis treatment are to halt curve progression, to prevent respiratory dysfunction and spinal pain syndromes, and to improve aesthetics via postural correction[2].

Brace treatment

Non-surgical treatment strategies for scoliosis were already widely practiced in Greek antiquity[14]. Hippocrates (460-370 B.C.) recommended, for example, diet and extension as a treatment for spinal deformities. He was probably the first who invented devices for correction of curvature based on axial traction and three points correction, such as the Hippocratic ladder, the Hippocratic board, and the Hippocratic bench[14]. Two and a half millennia later, bracing during the growth period is the best proven non-surgical treatment for idiopathic scoliosis, in which the three pressure point principle is still one of the basic mechanisms to achieve curve correction[2, 15-18].

The main therapeutic goal of brace treatment is to halt curve progression and prevent the need for surgical correction[2]. A cochrane review, published in 2015, concluded that bracing indeed prevent curve progression, but a good estimate of the effect remains uncertain due to the strength of evidence varying from moderate to very low, owing to the methodological qualities of the studies[18]. One included randomized and preference cohort trial reported a number needed to treat of 3 to prevent one case of curve progression requiring surgery[17].

The best proven predictive factors associated with brace treatment failure are lack of initial in-brace correction and decreased brace wearing time[19]. Several potential factors influencing initial in-brace correction have been described in literature, but there is no clear overview of all evaluated factors available yet.

During brace treatment, patients visit the outpatient clinic every six months and radiographs are made to monitor the curve. Besides monitoring of the curve, the brace fit must be checked routinely during the follow-up moments in order to maintain the best possible in-brace correction. This has resulted in a discussion whether these regular follow-up radiographs should be taken out-of-brace or in-brace. This has resulted in a discussion whether these regular follow-up radiographs should be taken out-of-brace or in-brace. On the one hand, follow-up with in-brace radiographs has the advantage that proper fit of the brace and in-brace correction can be evaluated, but on the other hand detection of progression might be theoretically more difficult, since the curve is partially corrected by the brace. Thirdly, brace compliance should be evaluated each follow-up moment as there was found a significant positive association between number of hours of brace wear and rate of treatment success[17, 20]. Since many factors are likely to contribute to the generally low compliance rates, the use of a disease-specific health-related quality of life (HRQOL) measuring instrument routinely at the outpatient clinics might potentially help with early detection of problems in different HRQOL domains in order to improve compliance.

In the last few decades, many different braces have been developed for scoliosis, but there are only few studies comparing those in literature[2, 21-25]. Also computer-aided design and manufacturing systems (CAD/CAM) combined with or without finite element models (FEM) simulation have been developed to replace the conventional plaster-cast method, but the added value for improved in-brace correction, brace comfort and compliance, compared to a conventional plaster-cast method are still relatively unknown. While a multidisciplinary group of international bracing experts has recently reached consensus on the best practice guidelines for the use of bracing in AIS, there is no evidence based consensus on the best possible manner to achieve curve correction with bracing [2, 21, 26]. Braces for scoliosis are still handcrafted products where experience and even intuition play an essential role, representing more the art than the science of medicine[21]. The results of brace treatment depend on the design and fabrication skills of the orthotist, the physician in prescribing and checking the brace, the compliance of the patient, and rest of the scoliosis treatment team in empowering the patient and family[21].

Generally, brace treatment is initiated if the major curve Cobb angle exceeds 20-25 degrees and continued until the end of spinal growth. Since the main goal of brace treatment is to halt curve progression, and the risk of progression is related to growth and the severity of the curve, knowledge about a patients' individual spinal growth spurt and its velocity might contribute in predicting curve progression and determining the best moment to start and end brace treatment[2, 10-13, 27]. So far, spinal length measurements are usually performed on coronal radiographs. Due to the complex three-dimensionality of the deformity, this could, however, influence the accuracy of growth measurements. Three-dimensional measure methods for spine length would therefore be of great value for both clinical and research purposes.

Surgical management of idiopathic scoliosis

Severe idiopathic scoliosis curves with a major curve Cobb angle exceeding 45-50 degrees have a high risk of progression in adulthood and are therefore usually treated surgically[11, 28, 29]. Posterior spinal instrumentation and fusion with pedicle screws at the end of the growth period is in those cases the standard practice in most scoliosis centers[30-33]. The main goals of the surgery are to correct the spinal deformity and to stabilize the spinal curves, while accounting for the overall spinal balance[33]. The amount of scoliosis correction that can be achieved during surgery is related to multiple patient, implant and surgeon factors, including inherent spinal flexibility and the direction and magnitude of forces applied[34]. Appropriate placement of well-sized pedicle screws is a prerequisite in order to bring significant corrective forces towards the spine. This can, however, be challenging in scoliosis due to vertebral rotation and the different morphometric characteristics of the pedicle dimensions[31]. As there is a wide variation in pedicle shapes and sizes in a scoliotic spine, screw misplacements and under- or oversizing is a nonnegligible risk[35]. This subsequently increases the risk of pedicle fracture, and screw loosening and even neurologic or vascular injury[36, 37]. Aside from the possible complications, the results of spinal fusion surgery for AIS are generally good with a relevant decrease in pain, and relevant improvements in functioning, self-image, and condition-specific and HRQOL[38].

AIMS AND OUTLINE OF THIS THESIS

The general aim of this thesis was to explore the possibilities of using a biplanar low-dose X-ray device as a tool for spine related measurements, and to expand the knowledge about factors associated with brace treatment success in adolescent idiopathic scoliosis. The thesis is divided in two parts. The first part focuses on radiographic analysis of the spine, and the second part focuses on bracing as non-operative management of scoliosis.

Part 1. Imaging

Knowledge about spinal length and subsequently growth of each individual AIS patient helps with accurate timing of both non-operative and operative treatment. So far, spinal length measurements are usually performed on coronal radiographs which has the disadvantages of radiographic beam divergence and not including deviations in the sagittal plane despite the fact that a scoliosis is a complex three-dimensional spine deformity[39]. Radiographs generated by a biplanar low-dose X-ray device (EOS®imaging, Paris, France) use substantially less radiation in comparison with computed tomography (CT) and conventional radiographs, have no divergence in the vertical plane, and allow 3D measurements using the EOS imaging software[40, 41]. **Chapter 2** describes a study investigating the validity and reliability of EOS two-dimensional (2D) and 3D spinal length measurements in patients with AIS.

The application of the EOS imaging system for spine related measurements was further investigated in a study described in **Chapter 3**. In this study the validity and intra- and interobserver reliability of preoperative EOS-images for pedicle size measurements in patients with idiopathic scoliosis were assessed. This could be of interest to scoliosis surgeons, since free-hand pedicle screw insertion methods are widely used for screw insertion during scoliosis surgery. Preoperative knowledge about the pedicle size helps then to maximize screw containment and minimize the risk of pedicle breach. Using standardized screw diameters for each spinal level or preoperative computed tomography (CT) as alternatives, for example, are not ideal, due to the variation in morphometric characteristics of the pedicle dimensions, and the exposure of this young population to high levels of radiation if using CT[35, 42]. With a reduced amount of radiation and no divergence in the vertical plane, the application of the EOS imaging system could therefore be potentially promising for pedicle size measurements[40, 41].

Part 2. Brace treatment

Rigorous bracing during the adolescent growth spurt can significantly decrease the progression risk and subsequent risk for surgical correction in AIS patients[2, 17]. Brace treatment is, however, not successful in every patient and there is room for further improvements[17]. Recently, strong evidence was found for the association between lack of initial in-brace correction and brace treatment failure[19]. For this reason, knowledge about factors influencing the initial in-brace correction would be interesting. In **Chapter 4** an overview of predictive factors on initial in-brace correction in idiopathic scoliosis patients and a best-evidence synthesis is presented.

Nowadays, many scoliosis braces are designed with computer-aided design and manufacturing systems (CAD/CAM) combined with or without finite element models (FEM) simulation[43]. Although initial in-brace correction is important for long-term brace treatment success, these methods do not significantly improve initial in-brace correction compared to the conventional plaster-cast method so far[43-46]. For better understanding of the brace technology it might be interesting to use these CAD technologies to quantify the trunk in 3D and brace characteristics. The degree of torso asymmetry and segmental peak positive and negative torso displacements are examples of parameters which can be analyzed with the use of the patient's 3D surface scans and brace models. **Chapter 5** describes a pilot study in which these torso asymmetry and torso displacements in a computer brace model are studied for potential correlations with initial in-brace correction in patients with AIS.

Besides initial in-brace correction, also compliance plays an important role in the success of a brace treatment as there was found a significant positive association between number of hours of brace wear and rate of treatment success[17, 20]. In a cross-sectional study determining motivations for compliance with brace therapy, it has been discovered that the patient's desire to avoid surgery and to prevent curve progression are the most important positive factors influencing brace compliance[47]. For this reason, early detection of curve progression during brace treatment could be essential for motivational reasons. The progression rate of a scoliosis curve can be assessed using regular follow-up radiographs, which can be taken out-of-brace or in-brace. Follow-up with in-brace radiographs has the advantage that proper fit of the brace and in-brace correction can be evaluated, but detection of progression might be theoretically more difficult, since the curve is partially corrected by the brace. As we could not find any studies in literature analyzing these two different radiographic follow-up strategies for the ability to detect curve progression and its rate, a retrospective study about this matter was conducted and presented in **Chapter 6.** In this study, two standardized protocols for follow-up radiographs (in-brace versus out-of-brace radiographs) from two different scoliosis centers were compared for the ability to detect curve progression over time in idiopathic scoliosis patients with failure of brace treatment.

During brace treatment for AIS, the generally low compliance rates remains a challenge for healthcare professionals. Many factors are likely to contribute to these low rates, including comfort, self-image, and social issues[48]. Further knowledge about the impact of brace wear and the effect of new brace modifications or brace-related interventions on different HRQOL domains could lead to new insights for better brace compliance. For this, a disease-specific HRQOL measurement, like the Brace Questionnaire (BrQ), is necessary[49]. The BrQ was developed as an instrument for measuring HRQOL of scoliosis patients undergoing brace treatment, and has been previously translated into different languages and validated, but had not yet been translated into the Dutch language[50-57]. **Chapter 7** describes a study investigating the validity and reliability of a translated and culturally adapted Dutch version of the BrQ.

Chapter 8 contains a general discussion on what has been achieved so far and discusses future perspectives. This thesis ends with a summary in **Chapter 9**.

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CHAPTER 2

Assessment of spine length in scoliosis patients using EOS imaging: a validity and reliability study

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Abstract

Purpose: Knowledge about spinal length and subsequently growth of each individual patient with adolescent idiopathic scoliosis (AIS) helps with accurate timing of both conservative and surgical treatment. Radiographs taken by a biplanar low-dose X-ray device (EOS) have no divergence in the vertical plane and can provide three-dimensional (3D) measurements. Therefore, this study investigated the criterion validity and reliability of EOS spinal length measurements in AIS patients.

Methods: Prior to routine EOS radiograph, a radiographic calibrated metal beads chain (MBC) was attached on the back of 120 patients with AIS to calibrate the images. Spinal lengths were measured from vertebra to vertebra on EOS anteroposterior (AP), lateral view and on the combined 3D EOS view (EOS 3D). These measurements were compared with MBC length measurements. Secondly, intra- and interobserver reliability of length measurements on EOS-images were determined.

Results: 50 patients with accurately positioned MBC were included for analysis. The correlations between EOS and MBC were highest for the 3D length measurements. Compared to EOS 3D measurements, the total spinal length was systematically measured 4.3% (mean difference=1.97 ±1.12cm) and 1.9% (mean difference=0.86 ±0.63cm) smaller on individual EOS two-dimensional (2D) AP and lateral view images, respectively. Both intra- and interobserver reliability were excellent for all length measurements on EOS-images.

Conclusion: The results of this study indicate a good validity and reliability for spinal length measurements on EOS radiographs in AIS patients. EOS 3D length measure method is preferred above spinal length measurements on individual EOS AP or lateral view images.

Introduction

Adolescent idiopathic scoliosis (AIS) is a common, complex three-dimensional (3D) deformity of the spine with a prevalence of 2-3%[1, 2]. The deformity develops during childhood and progresses severely in 0.1-0.3% of the diagnosed adolescents[2]. High (spinal) growth velocity during early pubertal growth spurt is a predisposing factor for a rapid increase of the deformity[3-5]. Since the risk of progression is related to growth and the severity of the curve, knowledge about spinal growth in each patient can help guiding both conservative and surgical treatment in these children. So far, spinal length measurements are often done on coronal radiographs which has the disadvantage of X-ray beam divergence and not including deviations in the sagittal plane[6]. Due to the complex 3-dimensionality of the deformity, this could influence the accuracy of growth measurements[6]. Routine computed tomography (CT) scans would allow 3D measurements. However, this is not an option due to the exposure of this young population to high levels of radiation and future risks of cancer[7]. The EOS® imaging system can provide biplanar low-dose radiographs of the whole spine at once, which reduces the amount of radiation substantially in comparison conventional radiographs[8, 9]. The system uses a C-arm so that images have no divergence in the vertical plane allowing more accurate 3D measurements. Despite these advantages, the reliability of EOS 3D measurements for spinal length assessment has not been investigated. Therefore, the aim of this study was to assess the validity and intra- and interobserver reliability of EOS spinal length measurements in patients with AIS.

Methods

Patients

This study was approved by the Medical Ethical Review Board (RR-number: 201800763) and executed in a tertiary care center for scoliosis. Patients were prospectively included from October 2018 to April 2020 after obtaining written informed consent. The inclusion criteria were: (1) patients aged between 12 and 30 years and (2) diagnosed with AIS with (3) a Cobb angle of the major thoracic or lumbar curve of 20 degrees or more. Patients with radiographs in brace, or previous spinal fusion surgery were excluded.

EOS *imaging*

Prior to the routine biplanar low-dose radiographs of the spine with the EOS system (EOS imaging, Paris, France), a radiographic calibrated chain with metal beads (5mm in diameter) was taped to the skin on the spinous processes from vertebra C7 to L5 (Figure 1)[8, 9]. The physician assistant (JB) placed the chain on the skin of all included patients by carefully palpating each individual spinous process to position the chain parallel to the curve before the patient was positioned on the EOS platform in standing position. Subsequently, the biplanar low-dose radiographs of the spine were conducted (Figure 2).

Two observers (CP and FW) independently examined the EOS images for eligibility. Only radiographs with the metal beads chain (MBC) positioned accurately over the spinous processes in parallel to the spine were included for analysis. Any differences or uncertainty concerning the inclusion of the radiographs was solved in a consensus meeting.

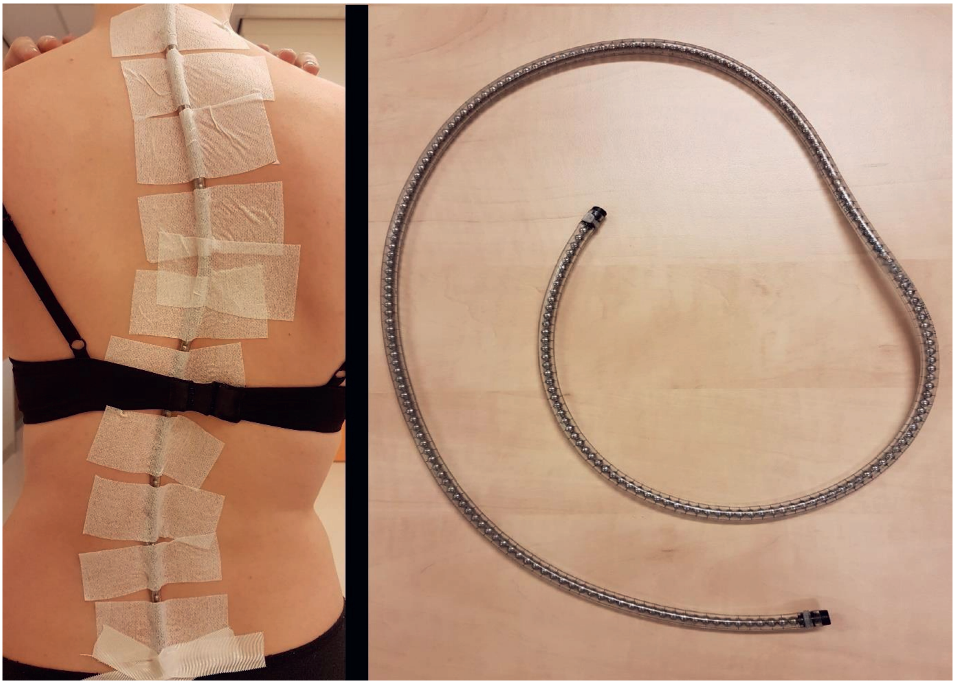

Figure 1: Radiographic calibrated chain with metal beads with a diameter of 5mm each, attached with tape over spinous processes from vertebra C7 to L5.

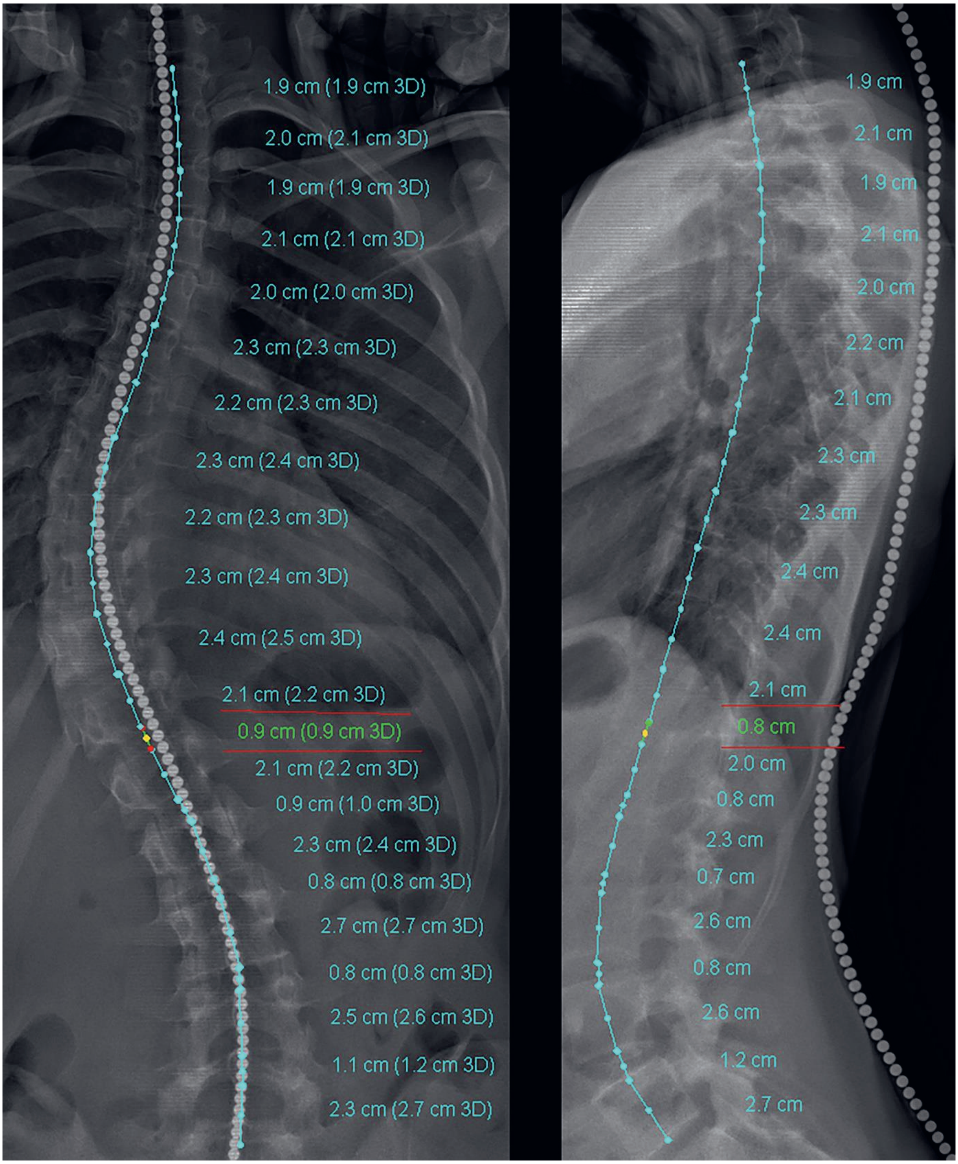

Figure 2: Anteroposterior and lateral view of EOS images with 2D and 3D spine length measurements using EOS system.

Method of measurements

Two independent observers (CP and JB) analysed the spine length from vertebra Th1 to L5 on the included EOS radiographs. Both observers were blinded for the scoring of the other observer. One observer (CP) performed all length measurements twice with at least a week between the measurements. For each segment, the distance between points was manually placed on the anteroposterior (AP) and lateral radiograph. For T12 till L5, points were positioned at the centre of each endplate on both the sagittal and coronal image. For levels T1 till T11, only the centre of the upper endplate was defined on both images. Since each point was placed in both projections using the EOS software, both two-dimensional (2D) and 3D spine height of the vertebral body (and intervertebral disc for T12 till L5) could be measured. The distance between all points was automatically measured by the software and the spinal length was defined by summing up all distances (Figure 2). The spinal length was measured in 2D (AP and lateral) and 3D. Subsequently, the number of metal beads visible on the AP radiograph was counted twice from vertebra Th1 to L5 and multiplied by 5mm. The metal beads were used to verify calibration of the distance on the X-ray and the sum of metal beads was used to compare the 2D and 3D total spine length in this study. The same measurement method was used for thoracic (lower edge T12 to upper edge T1) and lumbar (lower edge L5 to upper edge L1) spine length measurements to observe potential differences in accuracy between the thoracic and lumbar spine. Finally, MBC length calculations of spinal segments of at least 3 vertebrae with nearly perfect 3D parallel placement of the MBC were analysed separately to obtain most reliable segmental spine length calibration.

Statistical analyses

Spearman's rho correlation coefficients were calculated to determine the correlation between EOS 2D and 3D spine length measurements and spine length measurements obtained with the MBC. A Spearman's rho of 0.90-1.00 is considered to represent a very strong correlation, a Spearman's rho of 0.70-0.89 represents a strong correlation, 0.50-0.69 moderate, 0.26-0.49 weak, and <0.25 represents little or negligible correlation[10-12]. Criterion validity of EOS was evaluated with the Bland-Altman method using MBC as reference standard[13]. The data was checked for normal distribution. There is no systematic bias if the mean difference between the EOS and MBC length measurements is not significantly different from zero as assessed with a paired-sample T-tests. One-way ANOVA tests were used to assess the influence of major curve Cobb angle on the mean differences between MBC and EOS length measurements. For this the Cobb angle data was clustered in two groups (Cobb angle below or above 40 degrees).

The intra- and interobserver reliability and agreement were determined by calculating the intraclass correlation coefficients (ICCs) (two-way random, absolute agreement) and using the Bland-Altman method, respectively[13, 14]. For the intra- and interobserver reliability, an ICC greater than 0.9 is considered to represent excellent reliability, a value of 0.75-0.9 represents good reliability, 0.5-0.7 moderate, and an ICC less than 0.5 represents poor reliability[15]. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. A P-value <0.05 was considered to be statistically significant.

Results

Patient characteristics

Of the 120 patients fulfilling the inclusion criteria, 50 patients (41.7%) had good parallel placement of the MBC and were included for analysis. From one patient only the thoracic length measurements were included, since the placement on the lumbar curve was not considered accurate enough. The mean age of the 50 included patients at time of inclusion was 17.6 years (SD=3.3) with a range from 12 to 29 years. Forty-five patients (90%) were female. The mean Cobb angle of the major scoliosis curves was 35.7 degrees (SD=10.2, range=21.2-59.2).The mean Cobb angle of the thoracic scoliosis curves was 32.5 degrees (SD=12.4, range=9.8-59.2) and the mean Cobb angle of the lumbar curves was 24.1 degrees (SD=9.5, range=8.0-49.8).

Validity of EOS spine length measurements

The comparison of EOS (2D and 3D) and MBC spine length measurements is shown in Table 1 and Figure 3. Regarding the spinal segments of at least 3 vertebrae with parallel placed MBC for the most reliable segmental spine length calibration, all three EOS measure methods showed a very strong correlation with the MBC (Spearman's rho>0.99). No significant difference in spinal segment length was observed between EOS 3D and MBC measure methods (mean difference=0.03, 95% confidence interval=-0.03-0.10cm, P=0.35), but the spinal segments were systematically measured 3.1% and 1.1% smaller on EOS 2D AP and lateral view images, respectively, compared to MBC measurement (both P<0.01, Table 1).

Table 1: Comparison of EOS and MBC length measurements

Length measurement	N	Mean EOS (cm)	Mean MBC (cm)	Mean difference† (95% CI)	P-value	95% limits of agreement EOS - MBC	SDΔ	Spearman's rho
<u>Total spine</u>								
EOS 3D	49	45.68	45.09	0.59 (0.33 – 0.85)	<0.01*	-1.17 – 2.35	0.90	0.95
EOS 2D (AP)		43.71		-1.39 (-1.69 – -1.08)	<0.01*	-3.47 – 0.69	1.06	0.90
EOS 2D (lateral)		44.82		-0.27 (-0.57 – 0.02)	0.07	-2.27 – 1.73	1.02	0.89
<u>Thoracic spine</u>								
EOS 3D	50	27.65	27.16	0.49 (0.29 – 0.70)	<0.01*	-0.90 – 1.88	0.71	0.94
EOS 2D (AP)		26.62		-0.54 (-0.77 – -0.30)	<0.01*	-2.17 – 1.09	0.83	0.90
EOS 2D (lateral)		27.07		-0.09 (-0.31 – 0.14)	0.45	-1.64 – 1.46	0.79	0.90
<u>Lumbar spine</u>								
EOS 3D	49	17.21	17.12	0.09 (-0.10 – 0.28)	0.35	-1.18 – 1.36	0.65	0.75
EOS 2D (AP)		16.34		-0.78 (-0.96 – -0.60)	<0.01*	-2.01 – 0.45	0.63	0.78
EOS 2D (lateral)		16.95		-0.18 (-0.37 – 0.02)	0.08	-1.53 – 1.17	0.69	0.70
<u>Spinal segment‡</u>								
EOS 3D	39	11.62	11.58	0.03 (-0.03 – 0.10)	0.35	-0.36 – 0.42	0.20	>0.99
EOS 2D (AP)		11.22		-0.37 (-0.47 – -0.26)	<0.01*	-1.00 – 0.26	0.32	0.99
EOS 2D (lateral)		11.42		-0.16 (-0.27 – -0.06)	<0.01*	-0.79 – 0.47	0.32	>0.99

Length measurements are expressed in centimeters
†Mean difference was calculated by subtracting length measurements using MBC from EOS length measurements.
‡Spinal segments of at least 3 vertebrae with the most accurate placement of the metal beads chain.
**Represents a statistically significant difference (P<0.05)*
Abbreviations: 3D, three-dimensional; 2D, two-dimensional; AP, anteroposterior; N, number of patients; cm, centimeters; EOS, length measurements using EOS images; MBC, length measurements using metal beads chain; CI, confidence interval; SDΔ, standard deviation of mean difference.

Regarding the total spine length measurements, a very strong correlation was observed between EOS 3D and MBC (Spearman's rho=0.95), and EOS 2D (AP) and MBC (Spearman's rho=0.90) length measurements (Table 1). Strong correlation was found between EOS 2D (lateral view) and MBC length measurements (Spearman's rho=0.89). Significant differences in length measurements and a systematic bias were observed between EOS 3D and MBC, and EOS 2D (AP) and MBC. The total spinal length was systematically measured 4.3% smaller with EOS 2D AP measurement method (mean difference=1.97 ±1.12cm) compared to the EOS 3D measurement.

The EOS 2D lateral measurements underestimated the spinal length with 0.86 ±0.63cm (1.9%) compared to the EOS 3D measurement.

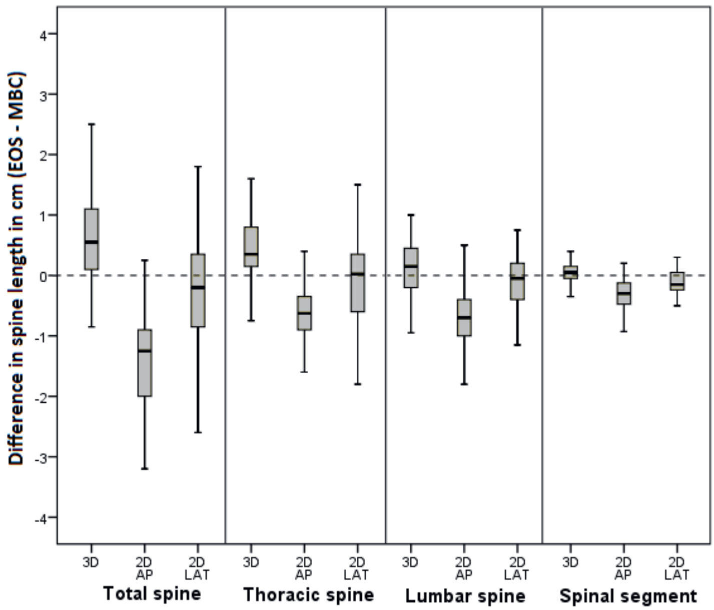

Figure 3: Box plots of the difference in length between the MBC measurements and the EOS 3D or EOS 2D (anteroposterior or lateral view) for the total, thoracic and lumbar spine, and for the 39 spinal segments.
Spine length measurements are expressed in centimeters.
Abbreviations: MBC, length measurements using metal beads chain; 3D, three-dimensional; 2D, two-dimensional; AP, anteroposterior.

When subdividing the data in thoracic and lumbar spine length measurements, very strong correlations were observed between thoracic spine MBC length measurements and all three EOS measurements, and strong correlations between lumbar spine MBC length measurements and all three EOS measurements (Table 1). Compared to EOS 3D measurements, the thoracic spine length was systematically measured 3.7% (mean difference=1.03 ±0.81cm) and 2.1% (mean difference=0.58 ±0.53cm) smaller with EOS 2D AP and lateral, respectively. The lumbar spine length was systematically measured 5.1% (mean difference=0.87 ±0.47cm) and 1.5% (mean difference=0.26 ±0.26) smaller with EOS 2D AP and lateral, respectively, compared to EOS 3D measurements.

Figure 4 presents box plots of the difference in total spine length between the MBC measurements and the EOS 3D or EOS 2D (AP or lateral view) of patients with a major curve Cobb angle below and above 40 degrees. The mean difference of EOS 2D (lateral view) and MBC length measurements was significantly larger for patients with a major curve Cobb angle exceeding 40 degrees (mean difference=-0.86 ±1.02cm), compared to patients with a major curve Cobb angle below 40 degrees (mean difference=0.04 ±0.88cm, P<0.01). No significant differences between the different major curve Cobb angle groups were observed for the comparison between MBC measurements and the EOS 3D (P=0.47) or EOS 2D AP (P=0.16). The comparisons of MBC and EOS measurements of total spine length of patients with or without a major curve Cobb angle exceeding 40 degrees are presented in supplementary data table 1.

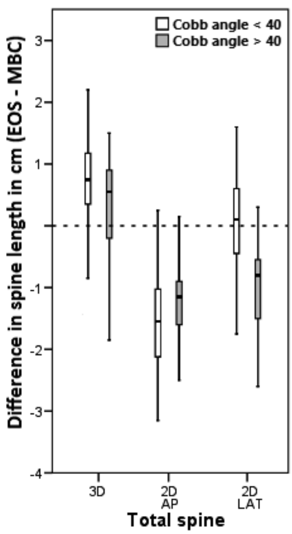

Figure 4: Box plots of the difference in total spine length between the MBC measurements and the EOS 3D or EOS 2D (AP or lateral view) of patients with a major curve Cobb angle below and above 40 degrees.
Spine length measurements are expressed in centimeters.
Abbreviations: MBC, length measurements using metal beads chain; 3D, three-dimensional; 2D, two-dimensional; AP, anteroposterior.

Intraobserver and interobserver reliability

Excellent intra- and interobserver reliability were established for all EOS 3D and 2D total, thoracic and lumbar spine length measurements (ICC's for intra- and interobserver reliability were respectively ≥0.91 and ≥0.96, Table 2-3). The mean intra-observer differences in length measurements varied between <0.01cm and 0.06cm, and were all not significant (Table 2). The 95% limits of agreement ranged from -1.47cm to 1.59cm. Regarding the interobserver agreement, the mean difference of length measurements varied between 0.01cm and 0.22cm, and the 95% limits of agreement ranged from -0.84cm and 1.02cm. A systematic bias was observed for the EOS 3D total spine (mean difference=0.14cm, 95% CI = 0.01–0.27cm), EOS 2D (AP) total spine (mean difference=0.22cm, 95% CI = 0.11–0.33cm), EOS 3D thoracic spine (mean difference=0.16cm, 95% CI = 0.05–0.27cm), and EOS 2D (AP) thoracic spine length measurements (mean difference=0.22, 95% CI = 0.14–0.31cm). There was no systematic bias between the two measurements of all EOS 2D (lateral view) length measurements and EOS 3D and 2D lumbar spine length measurements (Table 3).

Table 2: Intraobserver reliability of EOS length measurements

Length measurement	Mean M1 (SD)	Mean M2 (SD)	Mean difference† (95% CI)	P-value	95% limits of agreement M1-M2	SD Δ	SEM	SDC	ICC (95% CI)
Total spine									
EOS 3D	45.68 (2.63)	45.68 (2.68)	0.00 (-0.13 – 0.13)	1.00	-0.92 – 0.92	0.47	0.33	0.91	0.99 (0.97 – 0.99)
EOS 2D (AP)	43.71 (2.66)	43.64 (2.73)	0.06 (-0.16 – 0.29)	0.57	-1.47 – 1.59	0.78	0.55	1.52	0.96 (0.93 – 0.98)
EOS 2D (lateral)	44.82 (2.47)	44.83 (2.61)	-0.01 (-0.17 – 0.15)	0.90	-1.09 – 1.07	0.55	0.39	1.08	0.98 (0.96 – 0.99)
Thoracic spine									
EOS 3D	27.65 (1.56)	27.69 (1.56)	-0.03 (-0.14 – 0.07)	0.51	-0.74 – 0.68	0.36	0.25	0.69	0.97 (0.95 – 0.99)
EOS 2D (AP)	26.62 (1.57)	26.58 (1.67)	0.04 (-0.16 – 0.24)	0.69	-1.33 – 1.41	0.70	0.49	1.36	0.91 (0.84 – 0.95)
EOS 2D (lateral)	27.07 (1.44)	27.10 (1.54)	-0.02 (-0.15 – 0.10)	0.73	-0.88 – 0.84	0.44	0.31	0.86	0.96 (0.93 – 0.98)
Lumbar spine									
EOS 3D	17.21 (1.45)	17.19 (1.46)	0.02 (-0.05 – 0.10)	0.54	-0.53 – 0.57	0.28	0.20	0.55	0.98 (0.97 – 0.99)
EOS 2D (AP)	16.34 (1.40)	16.32 (1.42)	0.02 (-0.06 – 0.10)	0.54	-0.53 – 0.57	0.28	0.20	0.55	0.98 (0.97 – 0.99)
EOS 2D (lateral)	16.95 (1.42)	16.94 (1.47)	0.01 (-0.07 – 0.08)	0.87	-0.50 – 0.52	0.26	0.18	0.50	0.98 (0.97 – 0.99)

Length measurements are expressed in centimeters
†Mean difference was calculated by subtracting M2 from M1
**Represents a statistically significant difference (P<0.05)*
Abbreviations: 3D, three-dimensional; 2D, two-dimensional; AP, anteroposterior; M1, measurement 1 from observer CP; M2, measurement 2 from observer CP; CI, confidence interval; SDΔ, standard deviation of mean difference; SEM, standard error of measurement (SEM = SDΔ / √2); SDC, smallest detectable change (SDC = 1.96 x √2 x SEM) [16]; ICC, intraclass correlation coefficient.

Table 3: Interobserver reliability of EOS length measurements

Length measurement	Mean M1 (SD)	Mean M2 (SD)	Mean difference† (95% CI)	P-value	95% limits of agreement M1-M2	SD Δ	SEM	SDC	ICC (95% CI)
Total spine									
EOS 3D	45.68 (2.63)	45.54 (2.58)	0.14 (0.01 – 0.27)	0.04*	-0.74 – 1.02	0.45	0.32	0.89	0.98 (0.97 – 0.99)
EOS 2D (AP)	43.71 (2.66)	43.49 (2.61)	0.22 (0.11 – 0.33)	<0.01*	-0.51 – 0.95	0.37	0.26	0.72	0.99 (0.96 – 0.99)
EOS 2D (lateral)	44.82 (2.47)	44.77 (2.51)	0.04 (-0.09 – 0.18)	0.49	-0.84 – 0.92	0.45	0.32	0.89	0.98 (0.97 – 0.99)
Thoracic spine									
EOS 3D	27.65 (1.56)	27.49 (1.49)	0.16 (0.05 – 0.27)	0.01*	-0.60 – 0.92	0.39	0.28	0.78	0.96 (0.93 – 0.98)
EOS 2D (AP)	26.62 (1.57)	26.40 (1.53)	0.22 (0.14 – 0.31)	<0.01*	-0.37 – 0.81	0.30	0.21	0.58	0.97 (0.89 – 0.99)
EOS 2D (lateral)	27.07 (1.44)	26.97 (1.49)	0.10 (-0.01 – 0.21)	0.07	-0.66 – 0.86	0.39	0.28	0.78	0.96 (0.94 – 0.98)
Lumbar spine									
EOS 3D	17.21 (1.45)	17.22 (1.42)	-0.01 (-0.09 – 0.07)	0.84	-0.56 – 0.54	0.28	0.20	0.55	0.98 (0.97 – 0.99)
EOS 2D (AP)	16.34 (1.40)	16.33 (1.37)	0.01 (-0.07 – 0.08)	0.87	-0.50 – 0.52	0.26	0.18	0.50	0.98 (0.97 – 0.99)
EOS 2D (lateral)	16.95 (1.42)	17.00 (1.40)	-0.05 (-0.11 – 0.00)	0.07	-0.44 – 0.34	0.20	0.14	0.39	0.99 (0.98 – 0.99)

Length measurements are expressed in centimeters
†Mean difference was calculated by subtracting M2 from M1
**Represents a statistically significant difference (P<0.05)*
Abbreviations: 3D, three-dimensional; 2D, two-dimensional; AP, anteroposterior; M1, measurement 1 from observer CP; M2, measurement 2 from observer JB; CI, confidence interval; SDΔ, standard deviation of mean difference; SEM, standard error of measurement (SEM = SDΔ / √2); SDC, smallest detectable change (SDC = 1.96 x √2 x SEM) [16]; ICC, intraclass correlation coefficient.

Discussion

The results of this study show very strong correlations between EOS 3D and EOS 2D spinal length measurements and a calibration MBC placed over the spinous processes. Although perfect 3D parallel placement of the MBC over the full spinal length is not feasible due to the nature of the deformity, the spinal segments had a near perfect correlation (Spearman's rho >0.99) with the MBC indicating a good validity of the EOS system. The correlations were highest for the 3D measurements which respects the 3D nature of the deformity best. Both intra- and interobserver reliability were excellent for all length measurements on EOS-images.

In literature, spinal length measurements are often performed on coronal radiographs which have the disadvantage of X-ray beam divergence and not including deviations in the sagittal plane[6]. Due to the complex three-dimensionality of a scoliosis, 3D measurements could improve the accuracy of spinal length and growth measurements. In this study, the EOS 3D measurements resulted in the best representation of the spinal length. The MBC following the spinal curve resulted in a slight underestimation of the total spine length measurements with a small mean difference (0.59cm). The significant systematic bias between the two measure methods can be explained by the imperfection in parallel placement of the MBC as calibration chain for the complete spinal length measurements. The MBC was placed over the spinous processes and spinal length was measured at the center of the vertebral bodies. Because of this limitation in the calibration chain, short segments with almost perfect parallel placement of the MBC were included in this validation study. Compared to the EOS 3D length measurements, the EOS 2D measurements structurally underestimated the spinal length. This is not surprising since deviations in the other plane are not taken into account during the measurements of the 3D deformity. Compared to 3D, the 2D measurements on AP and lateral view resulted in 1.97cm (4.3%) and 0.86cm (1.9%) underestimation, respectively. Although the mean differences between 2D and 3D EOS measurement methods for total spine length were small, the EOS 3D length measure method could be preferred above spinal length measurements on individual EOS AP or lateral view images. When the EOS 3D length measurements are not possible, spinal length measurements on lateral view images could be preferred above measurements on AP view images if the coronal major curve Cobb angle is beneath 40 degrees. The 2D measurements on AP view resulted in a significant larger underestimation compared to 2D measurements on the lateral view ($P<0.01$). There was no significant difference between the two 2D measure methods if the coronal major curve Cobb angle was exceeding 40 degrees ($P=0.41$).

Clinical implications

Reliable spine length measure methods would be very useful in daily practice. Knowledge about the spinal growth of each individual patient helps with accurate timing of both conservative and surgical treatment, and is necessary to determine and demonstrate the performance of growth-friendly implants[6]. Based on the results, EOS 3D length measure method should be preferred above spinal length measurements on individual AP or lateral view images. It should particularly be considered in clinics where growth-friendly implants are used, since the patient's ability to grow with these implants is limited. Length measurements on lateral view images could be regarded as alternative when the coronal major curve Cobb angle is beneath 40 degrees.

Limitations

When interpreting the results of this study, a few limitations should be considered. There is no gold standard for spinal length measurements in AIS patients. A metal bead chain was taped over the spine for calibration in this study. However, it was difficult to place the MBC correctly on every single spinous process for parallel placement. Furthermore, the spinous processes are sometimes positioned closer to the midsagittal plane than the vertebral bodies due to the vertebral rotation in a scoliotic spine. Despite these limitations, the MBC was useful as reference for the spinal length measurements and validation of EOS using short segments. Another limitation of this study is that the measure method of spinal length on EOS radiographs is not standardized and therefore labor-intensive. Despite good intra and interobserver reliability, manual placement of measurement points may possibly be suboptimal because the visualization of vertebral endplates is not always good in the upper thoracic region due to overprojection of the shoulders. Ideally, this spinal length measurement would be captured in a 3D machine learning system. This would be less time-consuming and helpful in accurate planning of both conservative and surgical treatment.

Conclusion

In conclusion, this study shows a good validity and reliability for spinal length measurements on EOS radiographs. The EOS 3D length measure method is preferred above 2D spinal length measurements on EOS AP or lateral views and can be used for total, thoracic, lumbar or segmental spinal length measurements in AIS patients. When the EOS 3D measure method is not possible, spinal length measurements on EOS 2D (lateral view) could be preferred above measurements on EOS 2D (AP view) when coronal Cobb angle is below 40 degrees. In the future, an automated spinal length measurement system would be helpful in accurate timing of treatment.

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Supplementary data

Supplementary data table 1: Comparison of EOS and MBC total spine length measurements of patients with a major curve Cobb angle below or above 40 degrees

Total spine length measurement	N	Mean EOS (cm)	Mean MBC (cm)	Mean difference† (95% CI)	P-value	95% limits of agreement EOS - MBC	SDΔ	Spearman's rho
Major CA <40	32							
EOS 3D		45.13	44.48	0.65 (0.37 – 0.94)	<0.01*	-0.90 – 2.20	0.79	0.91
EOS 2D (AP)		42.93		-1.54 (-1.91 – -1.17)	<0.01*	-3.54 – 0.46	1.02	0.84
EOS 2D (lateral)		44.52		0.04 (-0.28 – 0.36)	0.80	-1.68 – 1.76	0.88	0.85
Major CA >40	17							
EOS 3D		46.71	46.25	0.46 (-0.11 – 1.03)	0.11	-1.72 – 2.64	1.11	0.95
EOS 2D (AP)		45.16		-1.09 (-1.67 – -0.52)	<0.01*	-3.29 – 1.11	1.12	0.92
EOS 2D (lateral)		45.39		-0.86 (-1.39 – -0.34)	<0.01*	-2.86 – 1.14	1.02	0.95

Length measurements are expressed in centimeters
†Mean difference was calculated by subtracting length measurements using MBC from EOS length measurements.
**Represents a statistically significant difference (P<0.05)*
Abbreviations: CA, Cobb angle; 3D, three-dimensional; 2D, two-dimensional; AP, anteroposterior; N, number of patients; cm, centimeters; EOS, length measurements using EOS images; MBC, length measurements using metal beads chain; CI, confidence interval; SDΔ, standard deviation of mean difference.

CHAPTER 3

3

Assessment of pedicle size in patients with scoliosis using EOS 2D imaging: a validity and reliability study

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Abstract

Purpose: Free-hand pedicle screw insertion methods are widely used for screw insertion during scoliosis surgery. Preoperative knowledge about the pedicle size helps to maximize screw containment and minimize the risk of pedicle breach. Radiographs taken by a biplanar low-dose X-ray device(EOS) have no divergence in the vertical plane. The criterion validity and reliability of preoperative EOS-images for pedicle size measurements in patients with idiopathic scoliosis (IS) were investigated in this study.

Methods: Sixteen patients who underwent surgical treatment for IS were prospectively included. Intra- and extracortical pedicle height and width measurements on EOS-images were compared with reconstructed intra-operative 3D-images of the isthmus of included pedicles. Secondly, intra- and interobserver reliability of pedicle size measurements on EOS-images were determined.

Results: The total number of analysed pedicles was 203. The correlation between the EOS and 3D-scan measurements was very strong for the intra- and extracortical pedicle height, and strong for the intra- and extracortical pedicle width. There are however significant, but likely clinically irrelevant differences (mean absolute differences<0.43mm) between the two measure methods for all four measurements except for extracortical pedicle height. For pedicles classified as Nash-Moe 0, no significant differences in intra- and extracortical pedicle width were observed. Both intra- and interobserver reliability were excellent for all pedicle size measurements on EOS-images.

Conclusion: The results of this study indicate a good validity and reliability for pedicle size measurements on EOS-radiographs. Therefore, EOS-radiographs may be used for a preoperative estimation of pedicle size and subsequent screw diameter in patients with IS.

Introduction

Posterior spinal instrumentation and fusion with pedicle screws is a standard practice in the surgical treatment of severe idiopathic scoliosis (IS)[1-3]. It is regarded as a safe and effective procedure in the majority of the patients[4]. However, appropriate placement of well-sized pedicle screws can be challenging in scoliosis due to the different morphometric characteristics of the pedicle dimensions and vertebral rotation[2]. As shown in earlier CT studies, there is a wide variation in pedicle shapes and sizes in a scoliotic spine[5]. Consequently, screw misplacements and under- or oversizing is a risk. This subsequently increases the risk of neurologic or vascular injury, pedicle fracture, and screw loosening[6-7].

Free-hand pedicle screw insertion methods are widely used for screw insertion. Due to the variation in pedicle dimensions, it is not possible to use standardized screw diameters for each spinal levels. Previous studies showed that full containment of the screws within the cortical pedicle walls was achieved 69–94% with free-hand placement, and pedicle breach rates are reported at 9.7% - 17.1%[6-7]. Preoperative knowledge about the pedicle size helps to maximize screw containment and minimize the risk of pedicle breach. To accurately measure the pedicle sizes, a preoperative computed tomography (CT) scan is needed[8]. However, this is not done routinely in clinical practice due to the exposure of this young population to high levels of radiation. Plane radiographs as alternative has the disadvantage that there is divergence in both the horizontal and vertical planes.

The EOS imaging system can provide biplanar low-dose radiographs of the spine, which reduces the amount of radiation substantially in comparison with CT and conventional radiographs[9-10]. Furthermore, images have no divergence in the vertical plane since the system uses a C-arm. Despite these advantages, the reliability of the EOS imaging system for pedicle size measurements have not been investigated.

The purpose of this study was to assess the validity and intra- and interobserver reliability of preoperative EOS images for measurements of the pedicle heights and widths in patients with IS.

Methods

Patients

This study was approved by the Medical Ethical Review Board (RR-number:201800917) and carried out in the University Medical Center Groningen (UMCG). After obtaining informed consent, patients were prospectively included from October 2018 to April 2019. Inclusion criteria were: (1) IS patients aged between 12 and 25 years with (2) a Cobb angle of the thoracic and/or lumbar curve of 50 degrees or more (3) undergoing surgical correction. Patients with spinal anomalies or previous spine operations were excluded.

Medical imaging

Routine biplanar low-dose radiographs of the spine were made preoperatively with the EOS system (EOS imaging, Paris, France). Patients were positioned on the EOS platform in standing position. Surgical treatment was performed using routine intra-operative 3D imaging (Siemens Arcadis Orbic 3D C-arm) and navigation system (Stryker). These intra-operative 3D images were used as "gold standard" in this study.

Method of measurements

Two independent observers (CP and LH), residents from the department of orthopaedic surgery and radiology, analysed the pedicle sizes in the preoperative EOS images and intra-operative 3D images. Both observers were blinded for the scoring of the other observer. One observer (CP) performed all measurements twice with a week between the measurements. The pedicle sizes were measured with Advanced PACS Viewer. The standing AP view was used for measurements on the EOS images. For the intra-operative 3D scan the vertical plane perpendicular on the lines of the transverse and sagittal pedicle angle was reconstructed at the narrowest part (isthmus) of each individual pedicle (figure1). The analysis of each pedicle consisted of the largest intracortical and extracortical diameter of the height and width of the pedicle isthmus (figures 1, 2). The Nash and Moe method was used on the EOS AP view to determine the vertebral rotation[11]. Pedicles on the concave side with a Nash-Moe rotation score ≥2 were not measurable and therefore excluded from analysis.

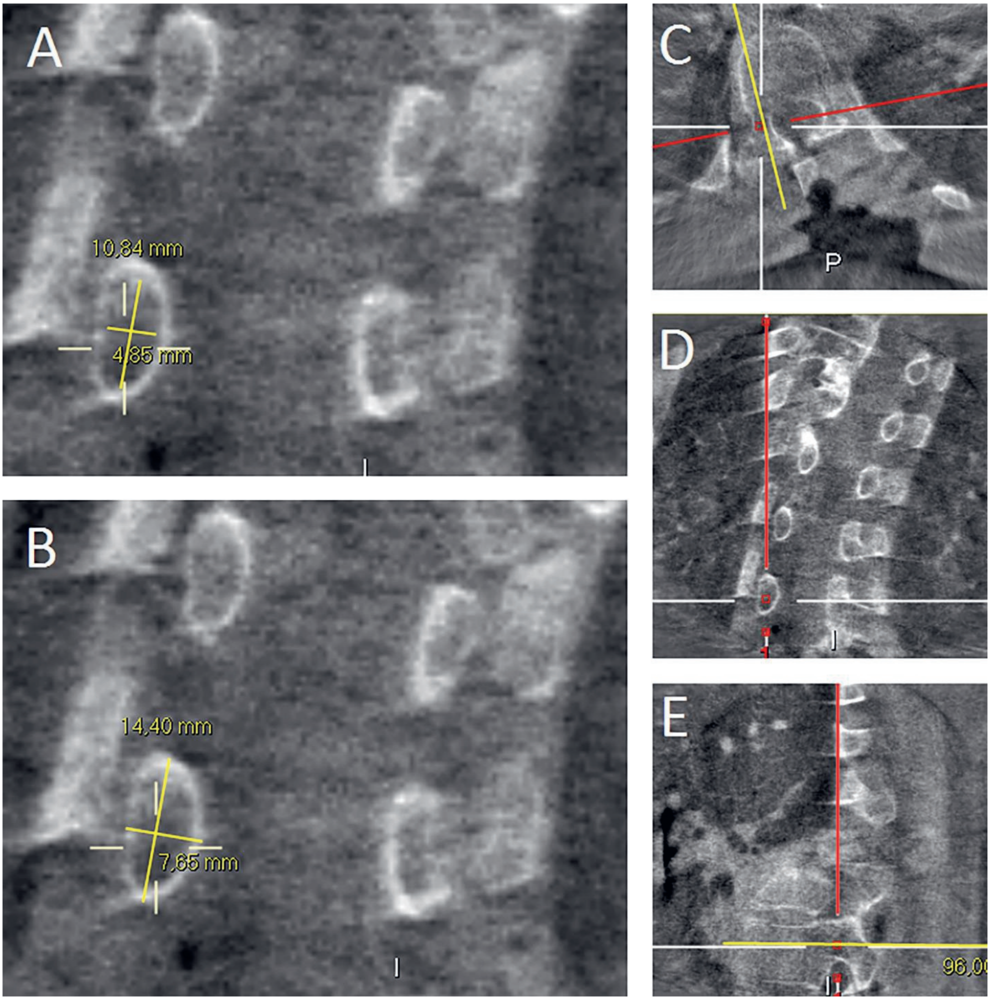

Figure 1: Intracortical (A) and extracortical (B) pedicle height and width measurements on.intra-operative 3D images. The vertical plane (D) on the lines of the transverse (C) and sagittal pedicle angle (D) was reconstructed at the narrowest part (isthmus) of each individual pedicle

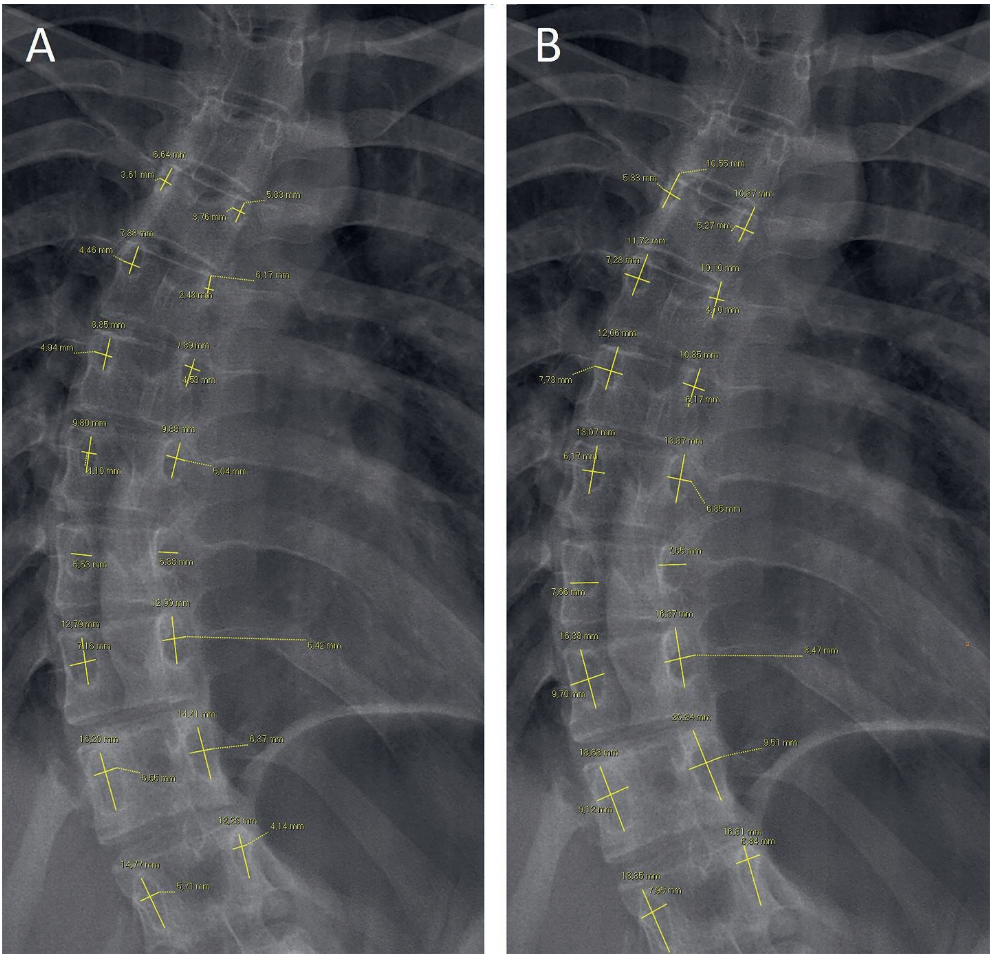

Figure 2: Intracortical (A) and extracortical (B) pedicle height and width measurements on preoperative EOS images.

Statistical analyses

Paired-sample T-tests were used to compare differences in the mean pedicle size measurements between EOS images and intra-operative 3D images measurements. Spearman's rho correlation coefficients were calculated between intra- and extracortical pedicle height and width measurements on EOS and intra-operative 3D images. A Spearman's rho of 0.90 - 1.00 indicates a very strong correlation, a rho of 0.70-0.89 indicates a strong correlation, 0.50-0.69 moderate, 0.26-0.49 weak, and <0.25 indicates little if any correlation[12-13]. Absolute agreement was evaluated with Bland-Altman plots[14]. If the 95% confidence interval (CI) of the mean difference between the two measurements contains zero, then no systematic bias is present between the measurements on EOS and intra-operative 3D images[15].

ANOVA with post-hoc Tukey tests were used to assess the influence of Nash-Moe vertebral rotation score and spinal level on the mean differences between EOS and 3D pedicle size measurements. For this the data was clustered in three Nash-Moe groups (0, 1, and 2-3) and four spinal level groups (T3-T5, T6-T9, T10-L1, and L2-L5). Since there were only few pedicles with a Nash-Moe score 3, they were clustered with Nash-Moe score 2 as one group.

The relative and absolute intra- and interobserver reliability were determined. The relative intra- and interobserver reliability were assessed by calculating the intraclass correlation coefficients (ICCs) (two-way random, absolute agreement) for each intra- and extracortical pedicle height and width measurements on the EOS radiographs[15]. ICC greater than 0.9 indicates excellent reliability, values of 0.75-0.9 indicate good reliability, 0.5-0.7 moderate reliability, and ICCs less than 0.5 are considered to indicate poor reliability[16]. The Bland-Altman method was used to evaluate the absolute intra- and interobserver reliability[14]. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A P-value <0.05 was considered statistically significant.

Results

Patient inclusion and characteristics

Sixteen patients with a mean preoperative Cobb angle of 60 degrees (SD=6.8) and a mean age of 16 years (SD=2.6) were included in the study (Table 1). Fourteen patients (87.5%) were female. The total number of pedicles measurements for comparing EOS and 3D imaging was 203. Most patients (81%) had a right thoracic structural scoliosis. Sixty-one pedicles on the concave side with a Nash-Moe grade score ≥ 2 could not be measured.

Table 1. Characteristics of the included patients

Patient	Gender	Age (y)	CA (degrees)	Fusion levels	N pedicles	N pedicles Nash moe score: 0	(1)	[2]	{3}
1	F	14	70	T4 – L1	13	6	(3)	[3]	{1}
2	F	19	52	T4 – L1	12	2	(5)	[5]	{0}
3	F	13	58	T3 – L1	15	0	(13)	[2]	{0}
4	F	20	52	T4 – T12	16	4	(12)	[0]	{0}
5	F	15	60	T4 – T12	13	2	(7)	[4]	{0}
6	F	14	71	T4 – L4	16	2	(7)	[4]	{3}
7	F	14	70	T3 – L2	11	0	(8)	[2]	{1}
8	F	18	53	T4 – L1	11	3	(4)	[4]	{0}
9	F	17	64	T3 – T12	11	2	(3)	[6]	{0}
10	F	16	56	T3 – T11	14	6	(6)	[2]	{0}
11	F	15	60	T4 – L5	17	4	(8)	[5]	{0}
12	M	16	62	T4 – L1	14	6	(4)	[4]	{0}
13	F	22	65	T3 – T11	11	2	(6)	[3]	{0}
14	F	13	62	T4 – L1	11	3	(3)	[5]	{0}
15	F	15	54	T4 – T11	10	2	(5)	[3]	{0}
16	M	18	50	T9 – L4	8	2	(2)	[4]	{0}
Total					203	46	(96)	[56]	{5}

Abbreviations: F, female; M, male; y, years; CA, preoperative cobb angle; T, thoracic vertebra; L, lumbar vertebra; N pedicles, number of measured pedicles for the comparison between EOS and 3D imaging

Validity of EOS measurements

The correlation between the EOS and intra-operative 3D measurements was very strong for the intracortical pedicle height (Spearman's rho=0.93), and strong for the intra- (Spearman's rho=0.85) and extracortical (Spearman's rho=0.87) pedicle width (Table 2). Significant differences in intracortical pedicle height, intracortical pedicle width, and extracortical pedicle width between EOS and intra-operative 3D measurements were established. The Bland & Altman plots showed a systematic bias in all three measurements. The intracortical pedicle height was systematically measured larger on EOS images (mean height: 9.01 versus 8.64mm for EOS and 3D run respectively). The intra-and extracortical pedicle width were systematically measured smaller on the EOS images than on the intra-operative 3D images (Table 2).

There were no significant differences in extracortical pedicle height between the two measurement methods (Table 2). The Bland & Altman plot showed also no significant bias, and the correlation between the two measure methods was very strong (Spearman's rho=0.95). The mean difference of the pedicle size measurements between EOS and 3D varied between 0.06mm and 0.43mm.

Table 2. Comparison of EOS and intra-operative 3D measurements

Measurement	N	Mean EOS (mm)	Mean 3D (mm)	Mean difference† (95% CI)	SDΔ	Range of difference EOS - 3D	P-value	Spearman's rho
Intracortical pedicle height	192	9.01	8.64	0.36 (0.22 – 0.50)	0.98	-2.28 – 3.91	<0.01*	0.927
Extracortical pedicle height	193	13.42	13.36	0,06 (-0.07 – 0.19)	0.90	-2.62 – 3.66	0.36	0.948
Intracortical pedicle width	199	3.63	3.87	-0.23 (-0.34 – -0.12)	0.80	-3.03 – 1.58	<0.01*	0.852
Extracortical pedicle width	201	6.00	6.43	-0.43 (-0.57 – -0.30)	0.97	-3.68 – 2.09	<0.01*	0.870

Abbreviations: N, number of compared pedicles; mm, millimeters; SD, standard deviation; CI, confidence interval; SDΔ, standard deviation of mean difference; EOS, EOS images; 3D, intra-operative 3D images; P, P-value
†Mean difference was calculated by subtracting the intra-operative 3D measurements from the EOS measurements
**indicates a statistically significant difference (P<0.05)*

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Influence of Nash-Moe scores on mean differences between EOS and 3D

The comparisons of EOS and intra-operative 3D measurements of pedicles with a Nash-Moe score 0, 1, and 2-3 are presented in supplementary data 1 in the same way as table 2. The mean difference of EOS and 3D intracortical pedicle width measurements was significantly larger for pedicles with Nash-Moe score 2-3 (mean difference: -0.47mm), compared to pedicles with Nash-Moe score 0 (mean difference: -0.06, P=0.03) or Nash-Moe score 1 (mean difference: -0.16, P=0.04). No other significant differences between the Nash-Moe groups were observed.

Influence of spinal level on mean differences between EOS and 3D

The mean absolute difference between EOS and 3D intracortical pedicle width measurements was significant smaller for the group pedicles from spinal levels T3-T5, compared to pedicles from spinal levels T10-L1 (mean difference: 0.13 versus -0.35mm for T3-T5 and T10-L1 respectively, P=0.04). Also for extracortical pedicle width significant smaller mean absolute differences were established for pedicles from spinal levels T3-T5 (mean difference=0.02mm) and T6-T9 (mean difference: -0.29), compared to pedicles from spinal levels T10-L1 (mean difference: -0.74mm, P=<0.01 and P=0.01 respectively). No other significant differences were found between the different spinal level groups. Box plots of the EOS and intra-operative 3D pedicle size measurements for each spinal level are presented in supplementary data 2-5.

Intraobserver and interobserver reliability

Relative intra- and interobserver reliability were excellent for all pedicle size measurements on

EOS (all ICC's ≥ 0.94, see table 3-4). The mean difference of the measurements varied between 0.02mm and 0.37mm. In the absolute intraobserver reliability analysis, there was no systematic bias between the two EOS intracortical pedicle height and width measurements. A systematic bias was observed in EOS extracortical pedicle height (95% CI=0.03–0.23mm) and width measurements (95% CI=0.01–0.17mm, see table 3). Regarding interobserver reliability, there was no systematic bias between EOS intracortical pedicle width measurements. For the EOS intra- (95% CI=0.27 – 0.47mm) and extracortical pedicle height (95% CI=0.05 – 0.27mm) and extracortical pedicle width (95% CI=0.15 – 0.31mm), a systematic bias was observed (Table 4).

Table 3. Intraobserver reliability of EOS measurements

Measurement	Mean M1 (SD)	Mean M2 (SD)	Mean difference† (95% CI)	SDΔ	SEM	SDC	Range of difference M1 – M2	P-value	ICC (95% CI)
Intracortical pedicle height	9.01 (2.48)	9.03 (2.55)	-0.03 (-0.13 – 0.06)	0.69	0.49	1.36	-2.15 – 2.74	0.49	0.96 (0.95 - 0.97)
Extracortical pedicle height	13.42 (2.82)	13.29 (2.86)	0.13 (0.03 – 0.23)	0.69	0.49	1.36	-1.91 – 2.44	0.01*	0.97 (0.96 – 0.98)
Intracortical pedicle width	3.63 (1.36)	3.65 (1.42)	-0.02 (-0.08 – 0.04)	0.41	0.29	0.80	-2.87 – 1.27	0.48	0.96 (0.94 – 0.97)
Extracortical pedicle width	6.00 (1.66)	5.91 (1.66)	0.09 (0.01 – 0.17)	0.57	0.40	1.11	-2.45 – 3.12	0.02*	0.94 (0.92 – 0.95)

Abbreviations: M1, measurement 1 from observer one (CP); M2, measurement 2 from observer one (CP); mm, millimeters; SD, standard deviation; CI, confidence interval; SDΔ, standard deviation of mean difference; SEM: standard error of measurement; SMC, smallest detectable change; P, P-value; ICC, intraclass correlation coefficient

†Mean difference was calculated by subtracting M2 from M1

**indicates a statistically significant difference (P<0.05)*

Pedicle height and width measurements are expressed in millimeters(mm)

Table 4. Interobserver reliability of EOS measurements

Measurement	Mean Ob 1 (SD)	Mean Ob 2 (SD)	Mean difference† (95% CI)	SDΔ	SEM	SDC	Range of difference Ob 1 – Ob 2	P-value	ICC (95% CI)
Intracortical pedicle height	9.01 (2.48)	8.64 (2.53)	0.37 (0.27 – 0.47)	0.72	0.51	1.41	-1.31 – 2.49	<0.01*	0.95 (0.90 – 0.97)
Extracortical pedicle height	13.42 (2.82)	13.26 (3.00)	0.16 (0.05 – 0.27)	0.78	0.55	1.52	-3.12 – 2.75	0.01*	0.96 (0.95 – 0.97)
Intracortical pedicle width	3.63 (1.36)	3.57 (1.39)	0.06 (<-0.01 – 0.13)	0.47	0.33	.91	-2.83 – 1.71	0.06	0.94 (0.92 – 0.96)
Extracortical pedicle width	6.00 (1.66)	5.77 (1.65)	0.23 (0.15 – 0.31)	0.55	0.39	1.08	-1.14 – 2.41	<0.01*	0.94 (0.90 – 0.96)

Abbreviations: Ob 1, measurement 1 from observer one (CP); Ob 2, measurement from observer two (LH); mm, millimeters; SD, standard deviation; CI, confidence interval; SDΔ, standard deviation of mean difference; SEM: standard error of measurement; SMC, smallest detectable change; P, P-value; ICC, intraclass correlation coefficient
†Mean difference was calculated by subtracting M2 from M1
**indicates a statistically significant difference (P<0.05)*
Pedicle height and width measurements are expressed in millimeters(mm)

3

Discussion

The results of this study show a very strong correlation between the EOS and intra-operative 3D measurements for the intra- and extracortical pedicle height, and a strong correlation for the intra- and extracortical pedicle width, indicating a good validity of EOS measurements. The mean absolute differences of the measurements between the two methods were small (0.06mm-0.43mm), but a systematic bias existed in all measurements, except for the extracortical pedicle height. The correlation was weaker but still strong for pedicles with a Nash-Moe score 2-3, compared to pedicles of vertebral bodies with less rotation. The mean absolute differences were often smaller for pedicles from higher spinal levels, what could be explained by the generally smaller pedicle sizes. Both intra- and interobserver reliability were excellent for all pedicle size measurements on EOS images.

A stronger correlation between EOS and intra-operative 3D measurements was observed for pedicle height measurements (very strong correlation) compared to pedicle width measurements (strong correlation). In particularly, pedicles with a Nash-Moe score 2 or 3 showed weaker correlation for the intra- and extracortical pedicle width measurements. This was expected for two reasons. First, the EOS imaging system uses a C-arm with the result that there should be no divergence in the vertical plane, but there still is in the horizontal plane. Vertebral bodies with pedicles with Nash-Moe score 2 and 3 are generally positioned closer to the apex of the scoliosis curve and therefore wider from the C7 plumb line than vertebral bodies with less rotation. Consequently, these pedicles near the apex have theoretically a more adverse effect of the divergence in the horizontal plane. Since there was a systematically measured smaller intra- and extracortical pedicle width of Nash-moe 2 and 3 pedicles (mean difference was -0.47mm and -0.51mm for intra- and extracortical pedicle width measurements, respectively) and no significant difference for pedicles classified as Nash-Moe 0 on the EOS images compared to intra-operative 3D images, the adverse effect of the divergence by the EOS imaging system was not regarded as a relevant factor and vertebral rotation is a more logic explanation for this systematic underestimation.

The transverse and sagittal pedicle axis lines have been described as the ideal pedicle screw trajectory in which each pedicle appeared largest, and are used for pedicle screw placements with intra-operative 3D imaging and navigation systems[5,17-18]. Therefore, the vertical plane perpendicular on these two lines was reconstructed at the isthmus of each pedicle for the pedicle size measurements on the intra-operative 3D scans. The isthmus is the smallest part of the pedicle through which a pedicle screw is mostly placed, so the strong correlation between the pedicle size measurements on this vertical plane and size measurements on EOS images found in this study is of great interest for providing a preoperative indication of needed pedicle screw diameters. Although a commonly accepted criteria for pedicle screw diameter selection has not yet been proposed in literature, the systematic review of studies with recommendations by Solitro et al. (2019) reported a screw diameter ranging from 80% to a maximum value of 125% of the pedicle width[7,19-20]. The human cadaver study of Christodoulou et al. (2005) described that the outer screw diameter should match precisely the intracortical pedicle width without ever exceeding the extracortical pedicle width[21]. However, in pediatric populations, the recommendations for maximum screw diameter / pedicle width ratio ranged from 1.15 to 1.25[7]. These higher values were explained by the relative plasticity of the pedicle cortex in the pediatric spine[20,22].

Clinical implications

In daily practice, surgeons using free-hand pedicle screw insertion methods can preoperatively reliably measure intra- and extracortical pedicle widths on EOS radiographs for an indication of the needed pedicle screw diameters for those individual pedicles. They should, however, be aware of the small systematic underestimation of the pedicle width measurements on EOS images when measuring visible pedicles from rotated vertebrae. On the other hand, since pedicle screws generally differ 1mm in diameter sizes, these small underestimations are likely clinically irrelevant. Surgeons performing scoliosis surgeries with intra-operative 3D imaging and a pedicle screw navigation system could also benefit from preoperative knowledge of pedicle sizes, as for determining the optimal screw trajectory less resolution and therefore less radiation is needed, further reducing the intra-operative dose.

Limitations

Intra-operative 3D images were used as a standard technique for pedicle size measurements in this study. Although a preoperative CT is regarded as the gold standard, the intra-operative 3D rotational X-ray technique have also shown an accurate correspondence with anatomic sections[23]. In addition, the intra- and interobserver reliability were excellent for all pedicle size measurements on intra-operative 3D images (ICCs >0.95, see supplementary data 6-7). A limitation of measuring pedicle sizes on EOS radiographs is that not every pedicle of the scoliotic spine can be measured due to overprojection or vertebral rotation. Pedicles on the concave side with a Nash-Moe grade score ≥2, for example, cannot be measured. Unfortunately, the pedicle size of the convex pedicle at this vertebra is not representative for the contralateral concave pedicle due to the asymmetry in IS[5,24]. This pedicle asymmetry has also been found in this study when left and right-sided pedicle sizes were compared on the intra-operative 3D scans (results not shown).

Conclusion

In conclusion, the results of this study indicate a good validity and reliability for pedicle size measurements on EOS radiographs. For pedicles classified as Nash-Moe 0, no significant differences in intra- and extracortical pedicle width were observed, but when measuring pedicles with a Nash-Moe score >0 surgeons should be aware of a significant systematic small underestimation of the pedicle width measurements on EOS images. As a result, EOS radiographs may be used for a preoperative estimation of pedicle size and subsequent screw diameter in patients with IS.

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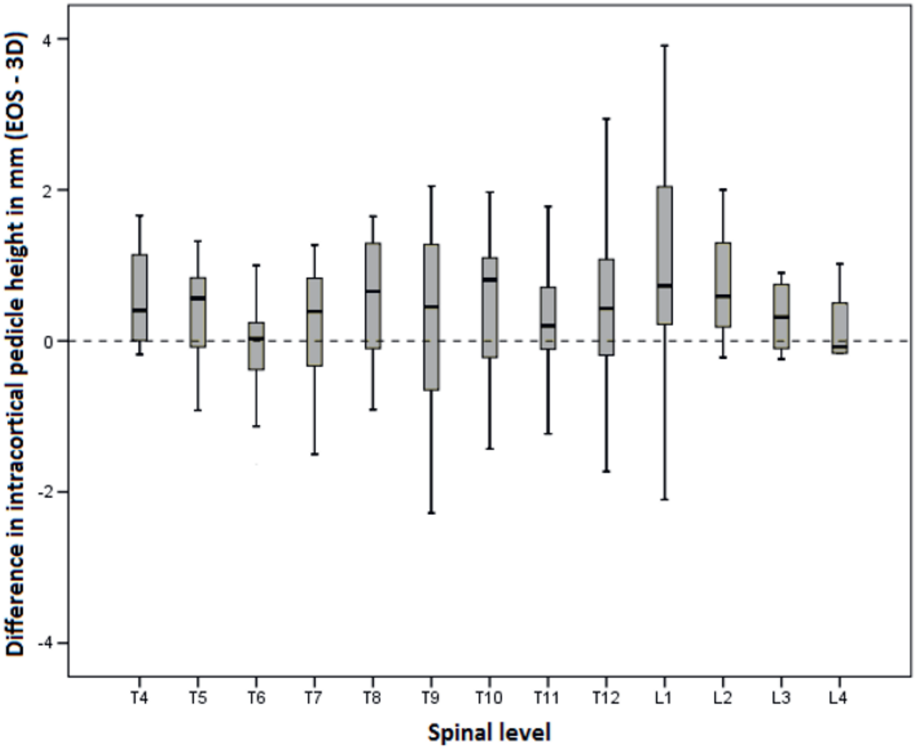
Supplementary data

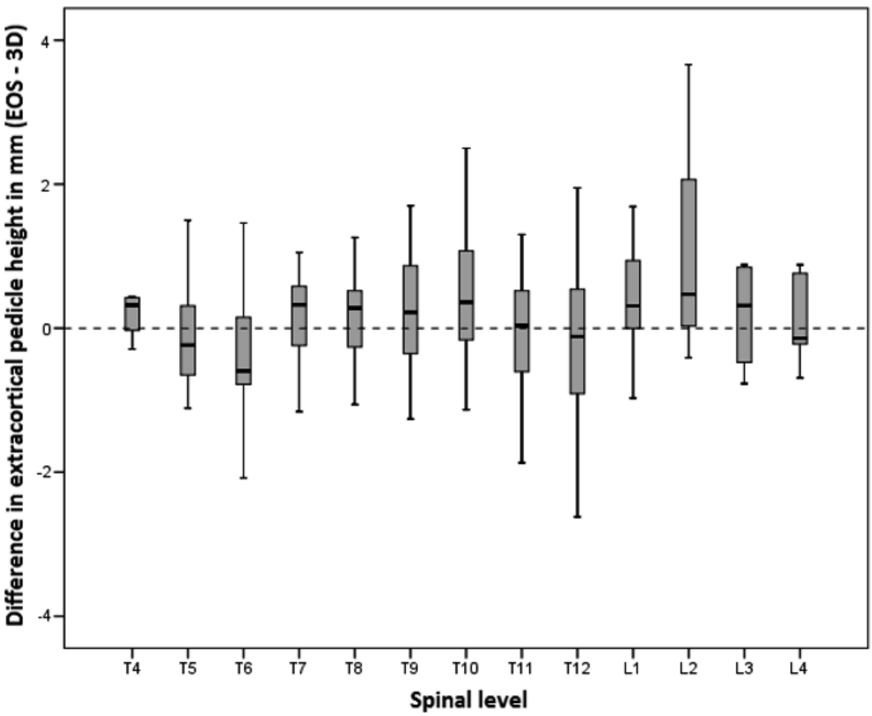
Supplementary data 1: Comparison of EOS and intra-operative 3D measurements of pedicles with a Nash moe score 0, 1, and 2-3

Measurement	N	Mean EOS (mm)	Mean 3D (mm)	Mean difference† (95% CI)	SDΔ	Range of difference EOS - 3D	P-value	Spearman's rho
Nash moe 0								
Intracortical pedicle height	42	9.68	9.19	0.49 (0.20 – 0.79)	0.94	-1,23 – 2.94	<0.01*	0.912
Extracortical pedicle height	42	13.89	13.98	-0.09 (-0.31 – 0.13)	0.72	-1.56 – 1.00	0.42	0.947
Intracortical pedicle width	42	4.25	4.30	-0.06 (-0.33 – 0.22)	0.88	-2.40 – 1.15	0.67	0.898
Extracortical pedicle width	43	6.68	6.80	-0.13 (-0.41 – 0.16)	0.92	-3.23 – 2.09	0.38	0.930
Nash moe 1								
Intracortical pedicle height	89	8.78	8.47	0.30 (0.09 – 0.52)	1.01	-2.28 – 2.93	0.01*	0.915
Extracortical pedicle height	90	13.07	13.08	-0.01 (-0.20 – 0.18)	0.90	-2.62 – 1.95	0.89	0.947
Intracortical pedicle width	95	3.60	3.76	-0.16 (-0.31 – <0.01)	0.76	-2.65 – 1.58	0.05	0.841
Extracortical pedicle width	96	5.91	6.43	-0.52 (-0.71 – -0.34)	0.91	-3.17 – 1.32	<0.01*	0.870
Nash moe 2-3								
Intracortical pedicle height	61	8.87	8.51	0.36 (0.11 – 0.61)	0.97	-2.10 – 3.91	0.01*	0.902
Extracortical pedicle height	61	13.62	13.35	0.27 (0.02 – 0.52)	0.98	-1.87 – 3.66	0.04*	0.912
Intracortical pedicle width	62	3.27	3.73	-0.47 (-0.66 – -0.28)	0.75	-3.03 – 1.38	<0.01*	0.814
Extracortical pedicle width	62	5.68	6.19	-0.51 (-0.78 - -0.24)	1.07	-3.68 – 1.80	<0.01*	0.774

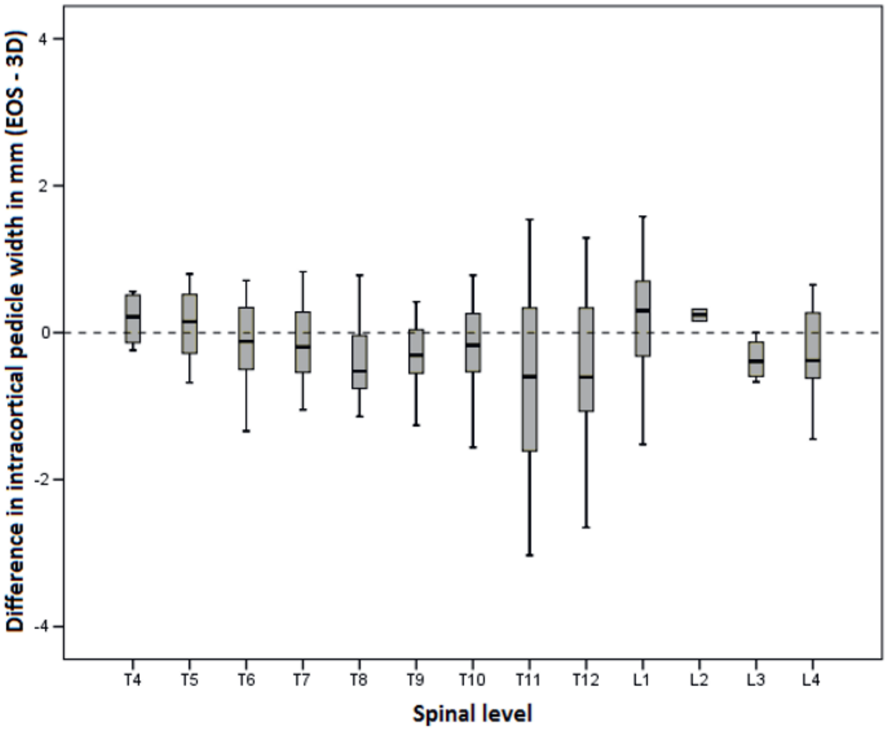
Abbreviations: N, number of compared pedicles; mm, millimeters; SD, standard deviation; CI, confidence interval; SDΔ, standard deviation of mean difference; EOS, EOS images; 3D, intra-operative 3D images; P, P-value
†Mean difference was calculated by subtracting the intra-operative 3D measurements from the EOS measurements
**indicates a statistically significant difference (P<0.05)*



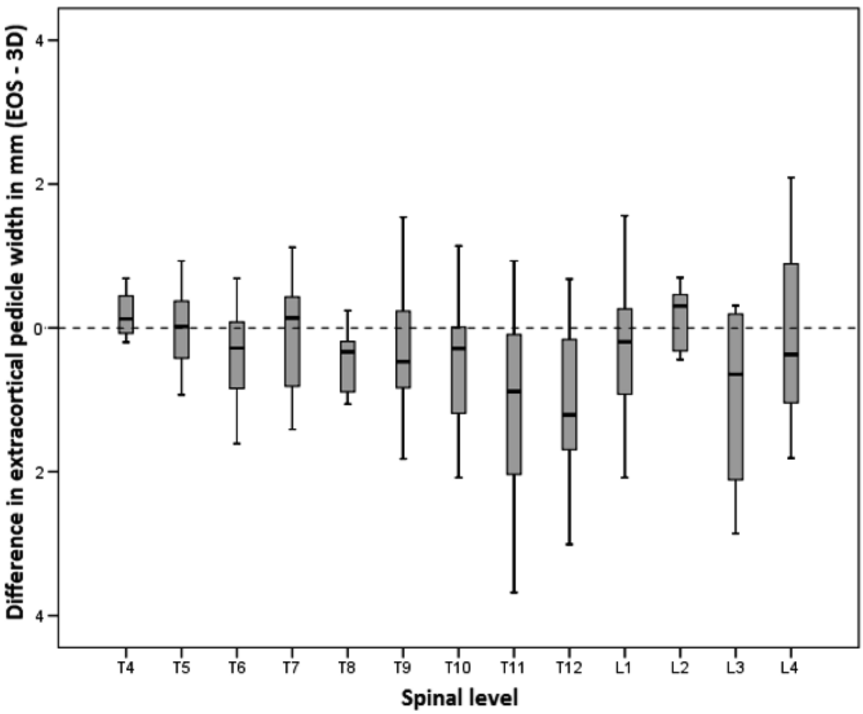
Supplementary data 2: Box plots of EOS and intra-operative 3D measurements of the intracortical pedicle height for each spinal level



Supplementary data 3: Box plots of EOS and intra-operative 3D measurements of the extracortical pedicle height for each spinal level



Supplementary data 4: Box plots of EOS and intra-operative 3D measurements of the intracortical pedicle width for each spinal level



Supplementary data 5: Box plots of EOS and intra-operative 3D measurements of the extracortical pedicle width for each spinal level

Supplementary data 6: Intraobserver reliability of intra-operative 3D measurements

Measurement	Mean M1 (SD)	Mean M2 (SD)	Mean difference† (95% CI)	SDΔ	SEM	SDC	Range of difference M1 – M2	P-value	ICC (95% CI)
Intracortical pedicle height	8.40 (2.53)	8.36 (2.65)	0.04 (-0.04 – 0.12)	0.64	0.45	1.25	-2.33 – 2.04	0.34	0.97 (0.96 – 0.98)
Extracortical pedicle height	12.97 (2.98)	13.00 (2.98)	-0.03 (-0.12 – 0.06)	0.75	0.53	1.47	-1.84 – 4.03	0.54	0.97 (0.96 – 0.98)
Intracortical pedicle width	3.69 (1.51)	3.84 (1.66)	-0.15 (-0.21 – -0.10)	0.45	0.32	0.89	-2.59 – 0.83	<0.01*	0.96 (0.93 – 0.97)
Extracortical pedicle width	6.02 (2.12)	5.94 (2.16)	0.08 (0.02 – 0.13)	0.48	0.34	0.94	-2.00 – 2.02	0.01*	0.98 (0.97 – 0.98)

Abbreviations: M1, measurement 1 from observer one (CP); M2, measurement 2 from observer one (CP); mm, millimeters; SD, standard deviation; CI, confidence interval; SDΔ, standard deviation of mean difference; SEM: standard error of measurement; SMC, smallest detectable change; P, P-value; ICC, intraclass correlation coefficient
†Mean difference was calculated by subtracting M2 from M1
**indicates a statistically significant difference (P<0.05)*
Pedicle height and width measurements are expressed in millimeters(mm)

Supplementary data 7: Interobserver reliability of intra-operative 3D measurements

Measurement	Mean Ob 1 (SD)	Mean Ob 2 (SD)	Mean difference† (95% CI)	SDΔ	SEM	SDC	Range of difference Ob 1 – Ob 2	P-value	ICC (95% CI)
3D Intracortical pedicle height	8.40 (2.53)	8.54 (2.61)	-0.14 (-0.23 – -0.05)	0.77	0.54	1.50	-2.34 – 2.15	<0.01*	0.95 (0.94 – 0.96)
3D Extracortical pedicle height	12.97 (2.98)	12.95 (3.03)	0.03 (-0.06 – 0.12)	0.79	0.56	1.55	-4.11 – 2.99	0.55	0.97 (0.96 – 0.97)
3D Intracortical pedicle width	3.69 (1.51)	3.81 (1.55)	-0.12 (-0.17 - -0.06)	0.47	0.33	0.91	-2.36 – 1.44	<0.01*	0.95 (0.94 – 0.96)
3D Extracortical pedicle width	6.02 (2.12)	5.80 (2.10)	0.22 (0.16 – 0.28)	0.52	0.37	1.03	-2.49 – 2.45	<0.01*	0.97 (0.94 – 0.98)

Abbreviations: Ob 1, measurement 1 from observer one (CP); Ob 2, measurement from observer two (LH); mm, millimeters; SD, standard deviation; CI, confidence interval; SDΔ, standard deviation of mean difference; SEM: standard error of measurement; SMC, smallest detectable change; P, P-value; ICC, intraclass correlation coefficient
†Mean difference was calculated by subtracting M2 from M1
**indicates a statistically significant difference (P<0.05)*
Pedicle height and width measurements are expressed in millimeters(mm)

3

CHAPTER 4

Predictive factors on initial in-brace correction in idiopathic scoliosis: a systematic review

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Abstract

Background: Brace therapy is the best proven non-surgical treatment for IS. There is strong evidence that lack of initial in-brace correction is associated with brace treatment failure. To improve initial in-brace corrections and subsequently long-term brace treatment success, knowledge about factors influencing initial in-brace correction is a prerequisite. The aim of this study was to systematically review the literature and provide an overview of reported predictive factors on initial in-brace correction in patients with idiopathic scoliosis (IS).

Methods: A systematic literature search was performed in Pubmed, Embase, Web-of-Science, Scopus, Cinahl, and Cochrane in November 2020. Studies which reported factors influencing initial in-brace correction in IS patients treated with brace therapy were considered eligible for inclusion.

Results: Of the 4562 potentially eligible articles identified, 28 studies fulfilled the inclusion criteria and were included in this systematic review. Nine studies (32%) were classified as high quality studies and the remaining 19 studies (68%) as low quality. Thirty-four different reported factors were collected from the included studies. Strong evidence was found for increased curve flexibility as favorable predictive factor for initial in-brace correction. Moderate evidence was found for thoracolumbar or lumbar curve pattern as favourable predictive factor, and double major curve pattern as unfavourable predictive factor for initial in-brace correction. Also moderate evidence was found that there is no significant difference on initial in-brace correction between computer-aided design and manufacturing systems (CAD/CAM) braces with or without finite element models (FEM) simulation, and braces fabricated using the conventional plaster-cast.

Conclusion: The results of this systematic review indicate that increased curve flexibility is strongly associated with increased initial in-brace correction.

Introduction

Idiopathic scoliosis (IS) is a complex three-dimensional deformity of the spine characterized by a lateral curvature of at least 10 degrees with vertebral rotation and often hypokyphosis[1]. Severe lateral curves exceeding 50 degrees in Cobb angle have a high risk of progression during adulthood and are therefore usually treated surgically[2]. To prevent surgical treatment, patients with smaller curves are treated with a brace during their adolescent growth spurt aiming to maintain the curve below 45-50 degrees[3]. Brace treatment can significantly decrease the progression risk and subsequent risk for surgical treatment in patients with adolescent idiopathic scoliosis (AIS). Unfortunately, bracing is not successful in every patient and the number needed to treat was 3 to prevent one case of curve progression requiring surgery.

Predictive factors for brace treatment outcome are recently evaluated in a systematic review[4]. Besides moderate evidence that increased brace wearing time is predictive for long-term treatment success, strong evidence was reported that lack of initial in-brace correction is associated with brace treatment failure[4]. In order to improve initial in-brace corrections and subsequently long-term brace treatment success, knowledge about factors influencing initial in-brace correction are a prerequisite. This systematic review provides an overview of reported predictive factors on initial in-brace correction in patients with IS.

Methods

Search strategy

A systematic literature search was performed in November 2020. Pubmed, Embase, Web-of-Science, Scopus, Cinahl (Ebsco), and Cochrane were used as databases to identify relevant studies since January 1995 up to November 2020. An overview of the search strategy is presented in *table 1*.

Table 1: Search strategy in Pubmed

(idiopathic[tiab] OR thorac*[tiab] OR lumbar*[tiab] OR adolescen*[tiab] OR juvenil*[tiab])
AND
(scoliosis[tiab] OR "scoliosis" [Mesh] OR ((spine[tiab] OR spinal[tiab]) AND deformit*[tiab]))
AND
("braces"[Mesh] OR brace*[tiab] OR braci*[tiab])

Inclusion and exclusion criteria

The studies retrieved from the literature search were included in this systematic review according to the following inclusion criteria: Patients were diagnosed with idiopathic scoliosis and treated with brace therapy (i), study described factors influencing initial in-brace correction (ii), full-text of the article was available (iii), and the study was published in English, Dutch or German (iv). Measure methods other than radiography, ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI) for initial in-brace correction, reviews, case reports, editorials, comments, letters, guidelines and protocols were excluded.

Study selection

Two reviewers (CP and AH) independently examined article titles and abstracts for eligibility. Subsequently, full text of potential studies were screened for final inclusion in this review. Any uncertainty concerning the inclusion of specific studies was solved in a single consensus meeting with a third reviewer (DK). In addition, reference lists of included papers were screened for eligible studies which were not identified by the electronic search.

Quality assessment

Two reviewers (CP and AH) independently assessed the methodological quality of each included study, using questions from the refined Quality in Prognosis Studies tool and Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[5, 6]. The 9 quality criteria are listed in table 2. Each item was assigned 'yes', 'no' or 'cannot determine', and scored one point for yes, and no point for no or cannot determine. If an item was described insufficiently, no point was assigned. Disagreements were solved by consensus. Consultation of a third reviewer (DK) in case of persistent disagreement was unnecessary.

Studies were defined as 'high quality' when at least 70% of the 10 items was assigned with one

point (≥7 points), and as 'low quality' when less than 70% (<7 points) was assigned with one point. The level of evidence was classified into the following levels[7-9]:
(1) Strong evidence: Generally consistent findings (≥75% of the studies showed results in the same direction) in at least two high-quality studies;
(2) Moderate evidence: Generally consistent findings (≥75%) in one high-quality study and at least one low-quality study, or consistent findings in multiple (≥2) low-quality studies;
(3) Insufficient evidence: only one study available or inconsistent findings in multiple (≥2) studies.

Table 2. Methodological quality criteria

Item	Score
1. A) Was a prospective evaluation of factors of influence on immediate in-brace correction stated? B) Were potential factors of influence on immediate in-brace correction predefined?	Yes / No / CD / NA Yes / No / CD / NA
2. Was the study population clearly specified and defined?	Yes / No / CD / NA
3. Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes / No / CD / NA
4. Was a sample size justification, power description, or variance and effect estimates provided?	Yes / No / CD / NA
5. Was the time frame between the without and in-brace images within two months?*	Yes / No / CD / NA
6. Method of prognostic factor measurement is adequately described, valid and reliable.	Yes / No / CD / NA
7. Was the immediate in-brace correction measured using Cobb's method on radiographs, CT or MRI in all patients?	Yes / No / CD / NA
8. Was the pre-treatment scoliosis curve and immediate in-brace correction verified independently?	Yes / No / CD / NA
9. Was loss to follow-up after baseline 20% or less?	Yes / No / CD / NA

*This timeframe was arbitrarily chosen, because the longer the time frame, the less reliable would be the outcome due to potential progression of scoliosis curve.
Abbreviations: CD, cannot determine.

Data extraction and presentation

Two reviewers (CP and AH) extracted the data of included studies. Information was collected on study design, study population, outcome measures, measure instrument for in-brace correction, time frame, and study results. All included studies are listed in a table and potential factors influencing initial in-brace correction are documented in the results.

Results

Study inclusion and characteristics

The literature search in the databases yielded 4562 studies after removal of duplicates (Figure 1). Finally, 28 studies fulfilled the inclusion criteria and were included in this systematic review[10-37]. An overview of the included studies is presented in table 3. A more comprehensive overview of the studies is presented in supplementary data 1.

The overall sample size of the included studies ranged from 6 to 182 patients[14, 21]. The mean age of the cohorts ranged from 6.9 (study including juvenile IS) to 14.2 years, and the gender of included patients was mainly female. In-brace correction was determined by radiography in 93% of the studies. One study used MRI and another used clinical ultrasound as instrument[10, 11]. The study's time interval between out-of-brace images or start brace wear and in-brace images for the determination of the curve correction varied between in-brace images within the same day and 6.5 months.

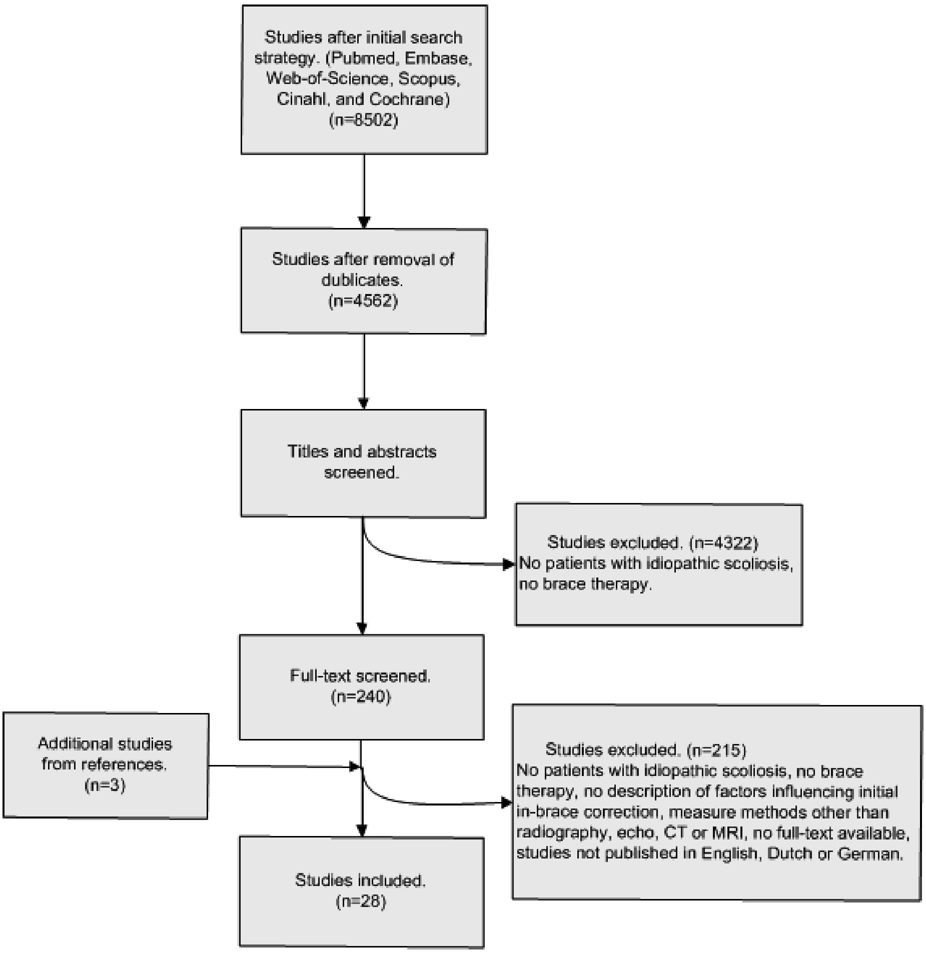

Figure 1: Study selection.

Table 3. Overview of reported predictive factors on initial in-brace correction

First author, year of publication	Design	QA	N	Age in years Mean ± SD (range)	% Male	Brace type	Instrument for measuring in-brace correction, and time frame*	Reported factor(s)	F	N	U
Cheung et al. 2018[18]	RS	H	105	12.2 ± 1.2	8%	Boston	X-ray; 2 weeks	Increased curve flexibility	X		
He, et al. 2017[23]	PS	H	35	12 ± 2	9%	RSO	X-ray; 2-3 weeks	Increased curve flexibility	X		
Labelle et al. 2007[25]	RCT	H	48	12.9 ± 1.4	4%	Boston	3D reconstruction from two X-rays; 3-4 weeks	Brace designed with computer-assisted tool compared to conventional plaster-cast method, higher Risser stage, increased pre-brace Cobb angle	X		
Hedayati, 2018[35]	PS	H	30	13.2 (8–17)	0%	Milwaukee	X-ray; 11 weeks	Brace adjustment twice per week and group exercise for 11 weeks	X		
Karam et al. 2019[36]	PS	H	52	12.4 ± 1.4	21%	-	Fulcrum bending X-ray; < 1day	A lateral force applied at the apical vertebra of the thoracic curve compared to a force placed at the apical rib	X		
Ohrt-Nissen et al. 2016[30]	RS	H	127	13.6 ±1.5	11%	Providence	X-ray; NA	Increased curve flexibility	X		
								Thoracic or double major compared to thoracolumbar and lumbar curve types			X
Guy, 2021[34]	RCT	H	120	13 (10- 16)	NA	TLSO	EOS X-ray; 5.7 months	Braces designed with CAD/CAM-FEM method compared to CAD/CAM alone		X	
Li et al. 2020[37]	RS	H	44	14.2 ± 2.4 (6–18)	18%	Chêneau	X-ray; 2 months	Increased apical rotate factor, increased pelvic rotate factor in patients with lumbar IS			X
								Lumber lordosis factor, coronal balance factor, vertical balance factor, pelvic symmetry factor		X	
Lang et al. 2019[29]	RS	H	119	12.6 ± 1.16 (10–15)	15%	Gensingen	X-ray; <6 weeks.	Curve type (thoracic vs. (thoraco)lumbar curves), age, gender, weight, height, BMI, Risser stage, menarche status		X	
								Increased C-DAR, increased pre-brace major CA			X
Lang et al. 2019[26]†	RS	L	112	12.6 ± 1.2 (10-15)	16%	Gensingen	X-ray; CD	Curve type (thoracic vs. (thoraco)lumbar curves), age, gender, weight, height, BMI, Risser stage, menarche status, RVAD, RVA-cx, RVA-cv		X	
								Increased LPR, spinal coronal or sagittal imbalance, increased pre-brace total (>55 degrees), major (>30 degrees) or minor curve CA			X
Boisvert et al. 2008[13]	RS	L	39	NA	NA	Boston	3D reconstruction from biplanar X-ray; <1 day	More severe scoliotic curve in the lower thoracic segment	X		
Chu et al. 2006[10]	PS	L	14	14 ± 1.0 (12 – 15)	0%	TLSO	MRI; <1 day	Prone position during assessment of initial in-brace correction, compared to other recumbent positions	X		
Bulthuis et al. 2008[16]	PS	L	63	11.3 ± 3.1	10%	TriaC	X-ray; 4 months	An increase in the continuous corrective force applied in a TriaC-brace	X		
Cobetto et al. 2016[19]	RCT	L	40	13.1 (10-16)	13%	TLSO	EOS X-ray; NA	Braces designed with CAD/CAM-FEM method compared to CAD/CAM alone	X		
D'Amato et al. 2001[20]	PS	L	102	NA (10-16.5)	0%	Providence	X-ray; NA	Increased curve flexibility, higher Risser stage (Risser 2 compared to Risser 0-1), curve apex below T8, primary thoraco-lumbar or lumbar curve pattern	X		

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Jarvis et al. 2008[24]	RS	L	23	8.3 years (5.5–9.9)	30%	Charleston	X-ray; 3 weeks	Single major curve type compared to double major and triple curve type in JIS, major curve of double major curve type compared to secondary curve in JIS	X		
Van den Hout et al. 2002[31]	PS	L	16	13.7 (8–17)	13%	Boston	X-ray; 6.5 months	An increase in mean compressive force over the thoracic or lumbar brace pad in a Boston brace		X	
Wong et al. 2005[32]	PS	L	40	12.6 (10 - 14)	0%	NA	X-ray; NA	Braces designed with CAD/CAM compared to conventional manual method		X	
Sankar et al. 2007[28]	PS	L	10	8.9	NA	TLSO	X-ray; 3 weeks	Braces designed with CAD/CAM compared to conventional plaster-cast method		X	
Desbiens-Blais et al. 2012[21]	PS	L	6	NA (11-13)	0%	TLSO	EOS X-ray; <1 day	Braces designed with CAD/CAM-FEM compared to conventional plaster-cast method		X	
Cobetto et al. 2014[22]	PS	L	15	NA (11-14)	0%	TLSO	EOS X-ray; NA	Braces designed with CAD/CAM-FEM compared to conventional plaster-cast method		X	
Al-aubaidi et al. 2013[15]	PS	L	24	12.8	0%	Providence	X-ray; 2 weeks	In- vs. outpatient protocols at the initiation phase of brace treatment		X	
Goodbody et al. 2016[14]	RS	L	182	12.5 ±1.4 (10-16)	14%	TLSO	X-ray; NA	BMI >85th percentile, BMI <20th percentile			X
Babaee et al. 2020[33]	RS	L	75	6.94 ± 1.86	24%	Milwaukee	X-ray; 4-6 months	Juvenile IS patients with Lenke type III curves, compared to Lenke type I, II, and V			X
Li et al. 2014[11]	PS	L	9	12.9	0%	NA	Clinical ultrasound; 1 day	Time in brace <2 hours before assessment of initial in-brace correction			X
Weiss et al. 2007[27]	PS	L	81	12.9 ± 1.9	NA	Cheneau light	X-ray; 6 weeks	Greater Age, higher Risser stage, increased pre-brace cobb angle			X
								Thoracolumbar and lumbar compared to thoracic or double major curve types	X		
Aubin et al. 1997[12]	PS	L	36	12.5 ±1.7	11%	Boston	3D reconstruction from two X-rays; 1-6 months	Transverse displacements of the rib cage, derotation forces on rib hump on frontal plane correction	X		
								Anterior displacements of the rib cage at apical level			X
Çhan et al. 2014[17]	PS	L	42	12.6 ± 1.0 (11-15)	0%	TLSO (HK brace)	X-ray; 4-6 months	Primary thoraco-lumbar curve pattern compared to thoracic curve pattern.	X		
								Brace compliance		X	

*Time frame between out-of-brace images or start brace wear and in-brace images for the determination of in-brace correction.

†This study probably included also patients from Lang et al. 2019[29]

Abbreviations: QA, quality assesment (High (H) or low quality (L) study according to QA, see table 2); N, number of patients; NA, not available; PS, prospective study; RS retrospective study; RCT, randomized and controlled trial; BMI, body mass index; vs.; versus; F, favourable predictive factor; N, non-influencing factor; U, unfavourable perdictive factor; RSO, rigid spinal orthosis; TLSO, thoracic lumbar sacral orthosis; RSC, Rigo System Chêneau brace; HK brace, Hong Kong brace; EOS, a low-dose digital radiography system; AIS, adolescent idiopathic scoliosis; FEM, finite element models; CAD/CAM, Computer-aided design and manufacturing systems; CA, Cobb angle; RVAD, rib vertebral angle difference; RVA-cx, rib vertebral angle - convex side, RVA-cv, rib vertebral angle - concave side; LPR, lumbo-pelvic ratio; C-DAR, coronal deformity angular ratio; SLBR, suspine lateral bending radiographs; MT, main thoracic; TL/L, thoraco-lumbar/lumbar; TK, thoracic kyphosis; LL, lumbar lordosis; ARF, apical rotate factor; PCPR, pelvic coronal plane rotation; AVR, apical vertebral rotation; PRF, pelvic rotate factor; PT, pelvic tilt; PI, pelvic incidence; LLF, lumber lordosis factor; PBF; coronal balance factor, VBF; vertical balance factor, PSF; pelvic symmetry factor.

Methodological quality

Nine studies (32%) were classified as high quality and the remaining 19 studies (68%) as low quality during quality assessment (Table 2 and supplementary data 2). The mean quality score was 5.2 (SD=2.2) with a range of 1 (low quality) to 9 (high quality). In 18 studies (64%) potential factors of influence on immediate in-brace correction were predefined. The methodological shortcomings mainly concerned items 4 (sample size justification), 8 (independently verified outcome measurements) and 9 (withdrawals and dropouts). Only six studies (21%) reported that the pre-treatment scoliosis curve and immediate in-brace correction was verified independently.

Factors associated with initial in-brace correction

An overview of 34 different reported factors is presented in table 3 and supplementary data 1. A best-evidence synthesis was performed to determine the strength of evidence of identified factors associated with initial in-brace correction (Table 4). Two studies from the same scoliosis center included 119 and 112 patients in the same time period and with comparable baseline characteristics[26, 29]. Since majority of the population in these studies overlapped, these two studies were regarded as one study for the best-evidence synthesis in case the same factors were reported.

Table 4. Overview of strong and moderate evidence predictive factors on initial in-brace correction

Level of evidence	Factor	F	N	U
Strong evidence†	Increased curve flexibility	X		
Moderate evidence‡	Thoracolumbar or lumbar curve pattern	X		
	Braces designed with CAD/CAM or CAD/CAM-FEM compared to conventional plaster-cast method		X	
	Double major curve pattern			X

†Generally consistent findings (≥75% of the studies showed results in the same direction) in at least two high-quality studies.
‡Generally consistent findings (≥75%) in one high-quality study and at least one low-quality study, or consistent findings in multiple (≥2) low-quality studies.
Abbreviations: F, favourable predictive factor; N, non-influencing factor; U, unfavourable perdictive factor; CAD/CAM, Computer-aided design and manufacturing systems; FEM, fenite element model.

Curve flexibility

Strong evidence was found for increased curve flexibility as favourable predictive factor for initial in-brace correction in 3 high quality studies and one low quality study[18, 20, 23, 30]. A strong correlation was found between the Cobb angle on a supine radiograph to assess curve flexibility and initial in-brace Cobb angle in 105 AIS patients treated with underarm bracing (Pearson correlation(r)= 0.74, P<0.001)[18]. Spinal flexibility assessed by ultrasound in the prone position in 35 AIS patients provided an effective method to predicts the initial in-brace correction in a brace. Prone position was found to be the closest and most correlated with initial in-brace correction (r=0.75) in this study[23]. Increased curve flexibility measured on supine lateral bending radiographs was also associated with increased in-brace correction in a Providence brace, and provided a very close estimation of the actual in-brace correction[30].

Curve pattern

Eight studies investigated the influence of scoliosis curve type on initial in-brace correction[17, 20, 24, 26, 27, 29, 30, 33]. Moderate evidence was found for double major curve type as unfavourable predictive factor for initial in-brace correction in patients with AIS or juvenile idiopathic scoliosis (JIS)[20, 24, 27, 30, 33]. One study reported less in-brace correction for the secondary curves (42%) compared to the major curves (85%) in 12 JIS patients with double major curve patterns[24]. Also moderate evidence was found for thoracolumbar or lumbar curve types as favourable predictive factor for initial in-brace correction compared to thoracic curve types[17, 20, 26, 27, 29, 30]. Four studies, including one of high quality, found significant less initial in-brace correction in AIS patients with thoracic curve type compared to thoracolumbar and lumbar curve types[17, 20, 27, 30]. The p-values for this factor were reported in 2 studies ($p<0.04$ and $p=0.002$)[17, 30]. However, two studies from the same group reported no significant difference in initial in-brace correction between thoracic and (thoraco)lumbar curve patterns ($p=0.79$ and $p=0.76$)[26, 29].

Brace related factors

Moderate evidence was found that there is no significant difference on initial in-brace correction between braces designed with computer-aided design and manufacturing systems (CAD/CAM) combined with or without finite element models (FEM) simulation, and braces fabricated using the conventional plaster-cast method[21, 22, 28, 32]. Only one high quality study reported a significant improvement of initial coronal curve correction in braces designed and adjusted with a 3D visualization software tool compared to conventional plaster-cast method ($p<0.01$ and $p=0.02$ for thoracic and lumbar curves, respectively)[25]. Insufficient evidence was found for the added value of CAD/CAM-FEM compared to CAD/CAM alone for initial in-brace correction[19, 34].

A high quality study discovered that a lateral force applied at the apical vertebra of the thoracic curve was significantly more efficient at correcting coronal deformity than a force placed at the apical rib ($p=0.001$)[36]. Furthermore, translations generated by the Boston brace system on the thorax generally are statistically and linearly related to corresponding corrections of the spine[12]. Derotation forces at the apex of the rib hump were found to be limited and did not allow the reduction of axial rotation (r=0.12), but were correlated with the reduction of spine offset in the frontal plane (r=0.43). Also a tendency was found that anterior displacements of the rib cage at apical level is accompanied by an increase of the spinal thoracic curve (r=-0.41, p=0.01)[12]. Insufficient evidence for a correlation between magnitude of the corrective force over the thoracic or lumbar brace pad and degree of in-brace correction of the major curve was found[16, 31].

Radiologic factors

Insufficient evidence was found for increased pre-brace major Cobb angle, rib vertebral angle difference (RVAD), rib vertebral angle-convex side (RVA-cx) , rib vertebral angle-concave side (RVA-cv), lumbar lordosis factor, coronal balance factor, vertical balance factor, and pelvic symmetry factor as influencing factors for initial in-brace correction[13, 25, 26, 27, 29, 37]. There is also insufficient evidence for higher Risser stage, curve apex below T8, increased lumbo-pelvic ratio (LPR), coronal deformity angular ratio(C-DAR), apical rotate factor, pelvic rotate factors, and spinal coronal or sagittal imbalance as predictive factors for initial in-brace correction[20, 25, 26, 27, 29, 37].

Other reported factors

Insufficient evidence was found for age, gender, height, weight, menarche status, and BMI as predictive factors for initial in-brace correction[14, 26, 27, 29]. A high quality study discovered that brace adjustment of a Milwaukee brace twice per week combined with group exercise under supervision of a skilled physiotherapist for 11 weeks resulted in significantly better initial in-brace Cobb angle curve correction, compared to a routine protocol in the control group (P=0.04)[35]. There is also a time lag between brace application and its effect on scoliotic curve[11]. The spinal response to brace application or removal seemed to plateau after approximately 120 minutes, and therefore radiographs should not be obtained within 2 hours after brace application or removal for the most reliable image. When assessing in-brace correction with a MRI, the largest in-brace correction in a thoracic lumbar sacral orthosis was observed when the patient is in prone position, compared to supine, right and left decubitus positions[10]. No significant difference on primary in-brace correction was reported between in hospitalization and outpatient clinic protocols, at the initiation phase of brace treatment with a Providence night time only brace[15]. Lastly, insufficient evidence was found for compliance

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as influencing factor for initial in-brace correction[17]. One study reported no significant difference on in-brace correction (<40% and ≥40% correction) after 4-6 months between three groups of different hours of brace wear (0–8 hours, 9–16 hours, and 17–23 hours)[17]. In this study brace wearing hours were recorded on a log sheet and by an orthosis monitoring system.

Discussion

This systematic review provides an overview of predictive factors on initial in-brace correction in patients with IS. Strong evidence was found for increased curve flexibility as favourable predictive factor for initial in-brace correction. Moderate evidence was found for thoracolumbar or lumbar curve pattern as favourable predictive factor, and double major curve pattern as unfavourable predictive factor for initial in-brace correction.

Although curve type and curve flexibility are patient factors which cannot be influenced by the orthotist, this information is useful to clarify differences in between patients. Less initial in-brace correction in a Providence for thoracic curve type and double major curves was seen compared to thoracolumbar and lumbar curve types[30]. However, when subsequently adjusted for curve flexibility, no difference in curve correction between curve types was found (P=0.77). This indicates that the differences in initial in-brace correction between curve types might be the result of differences in curve flexibility rather than the curve pattern itself[30]. Measuring curve flexibility can provide a very close estimation of the actual in-brace correction in clinical practice[18, 23, 30]. A high quality study reported a regression model (in-brace Cobb angle = 0.809 x supine Cobb angle) which could be used as a guide to determine initial in-brace correction[18]. Although a lack of initial in-brace correction is associated with brace treatment failure, a minimum threshold for in-brace correction has not been established[4]. Various cut-off values between <10% to 45% for initial in-brace correction have been reported to be predictive for brace treatment failure[4, 38].

Unlike curve type and flexibility, brace manufacturing technologies are factors that can be further optimised by the orthotists. So far, no significant differences in initial in-brace correction were seen between braces designed with CAD/CAM combined with or without FEM simulation, and braces fabricated using the conventional plaster-cast (moderate evidence). Although a CAD/CAM (/FEM) technology did not significantly improve initial in-brace correction compared to a conventional plaster-cast method, an added value of CAD/CAM (/FEM) braces on brace comfort was reported[22, 28]. Better brace comfort could improve compliance and subsequently brace treatment success. Furthermore, CAD technology can be useful to 3-dimensionally quantify the trunk and brace characteristics to further investigate the effect of brace modifications on initial in-brace correction.

This review has several strengths and limitations worth mentioning. A best-evidence synthesis was performed, since a meta-analysis could not be performed due to the heterogeneity of the included studies. This heterogeneity resulted also in insufficient evidence for most reported factors, mainly because factors were only studied once. The time frame between out-of-brace images or start brace wear and in-brace images to determine the correction varied between the same day and 6.5 months. Long time frame may generate a potential bias since curves could have progressed. Although in-brace correction plateaued after 120 minutes and shorter time frames decrease the risk of curve progression, patients should be adapted sufficiently to the brace to obtain an image with neutral posture[11]. Therefore, standardization of the time frame to determine in-brace correction would be beneficial. Another limitation of this study is that 25% of the included studies used absolute Cobb angle corrections instead of percentage curve corrections for analysis of initial in-brace correction. Ideally, future studies identifying potential predictive factors on initial in-brace correction should provide both absolute and percentage curve corrections.

Conclusion

In conclusion, the results of this systematic review indicate strong evidence for increased curve flexibility, and moderate evidence for thoracolumbar or lumbar curve pattern as favourable predictive factors for initial in-brace correction. Moderate evidence indicates that a double major curve pattern is an unfavourable predictive factor for initial in-brace correction. Braces designed with CAD/CAM or CAD/CAM-FEM did not result in improved initial in-brace correction compared to braces fabricated using the conventional plaster-cast method.

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Supplementary data 1. Overview of studies reporting predictive and non-predictive factors on initial in-brace correction in patients with IS

First author, year of publication	Design	QA	N	Age in years Mean ± SD (range)	% Male	Brace type	Reported factors	Instrument for measuring in-brace correction, and time frame*	Conclusions
Cheung et al. 2018[18]	RS	H	105	12.2 ± 1.2	8%	Boston	-Curve flexibility	X-ray; 2 weeks	A strong correlation was found between the Cobb angle on a supine radiograph to assess curve flexibility and initial in-brace Cobb angle (Pearson correlation(r)=0.74, P<0.001). This supports the significant influence of curve flexibility on the initial in-brace correction with underarm bracing. Age (P=0.50), weight (P=0.75), height (P=0.93), date of menarche (P=0.88), and Risser stage (P=0.44) were found not to be contributing factors to patient's curve flexibility.
He, et al. 2017[23]	PS	H	35	12 ± 2	9%	RSO	Curve flexibility	X-ray; 2-3 weeks	Spinal flexibility assessed by an ultrasound system in the prone position provides an effective method to predict the initial in-brace correction in a symmetric underarm rigid spinal orthosis, since this position was found to be the closest and most correlated with initial in-brace correction among four positions (supine (Pearson correlation(r)=0.66), prone (r=0.75), sitting (r=0.04) and prone with lateral bending (r=0.03)).
Labelle et al. 2007[25]	RCT	H	48	12.9 ± 1.4	4%	Boston	-Brace designed with computer-assisted tool -Risser stage -Pre-brace Cobb angle	3D reconstruction from two radiographs; 3-4 weeks	-Significant improvement of initial in-brace coronal curve correction was established in the group AIS patients with braces designed and adjusted with a 3D visualization software tool compared to the group patients with a Boston brace build with conventional plaster-cast method (P<0.01 and P=0.02 for thoracic and lumbar curves, respectively). -For Cobb angle of the thoracic curves in the plane of maximum curvature (Beta value 0.31, P=0.03) and the orientation of the plane of maximum curvature in the lumbar region (Beta value 0.41, P=0.01), skeletal maturity (Risser stage) also appeared to be associated with the spinal correction. -Initial in-brace correction of thoracic coronal Cobb angle depended also on initial out-of-brace deformity (Beta value 0.55, P<0.01).
Hedayati, 2018[35]	PS	H	30	13.2 (8–17)	0%	Milwaukee	Brace adjustment twice per week and group exercise.	X-ray; 11 weeks	Brace adjustment of a Milwaukee brace twice per week combined with group exercise under supervision of a skilled physiotherapist for 11 weeks resulted in significantly better initial in-brace Cobb angle curve correction, compared to a routine protocol in the control group (P=0.04). However, after adjusting for posttest Scoliosis Research Society questionnaire scores and posttest major Cobb angle magnitude using analysis of covariance, no significant difference between the two groups was esthablished.
Karam et al.	PS	H	52	12.4 ± 1.4	21%	-	Pad placement	Fulcrum bending	-A lateral force applied at the apical vertebra of the thoracic curve was

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2019[36]								radiograph; < 1day	significantly more efficient at correcting coronal deformity than a force placed at the apical rib (P=0.001). This difference was not related to patient age (P=0.90) or curve apex (P=0.81). In addition, the mean difference in absolute curve reduction between the two fulcrum positions was not statistically different among different Lenke type groups (P=0.266). In this study, a passive reaction force exerted by a fulcrum was used to simulate a lateral pressure force applied by the thoracic pad in a brace.
Ohrt-Nissen et al. 2016[30]	RS	H	127	13.6 ±1.5	11%	Providence	-Curve type -Curve flexibility	Radiograph; NA	-Cobb angle measured on suspine lateral bending radiographs (SLBR) was the same as initial in-brace correction obtained with a Providence brace (PB) brace, and therefore provides a very close estimation of the actual in-brace correction. -Significant less initial in-brace correction for thoracic curve type (P<0.04) and also less in-brace correction for double major curves was observed, compared to thoracolumbar and lumbar curve types. When adjusted for curve flexibility no difference in curve correction between curve types was found (P=0.77). Increased curve flexibility has been associated with increased in-brace correction.
Guy, 2021[34]	RCT	H	120	13 (10- 16)	NA	TLSO	Braced designed with CAD/CAM-FEM method	EOS radiograph; 5.7 months	No significant differences on initial in-brace coronal curve correction (P=0.05 for MT, P=0.91 for TL/L), sagittal curve reduction (P=0.43 for TK, P=0.70 for LL), and transverse apical rotation reduction (P=0.67 for MT, P=0.85 for TL/L), were found between the TLSO designed with CAD/CAM and FEM simulation and the TLSO designed with CAD/CAM alone.
Li et al. 2020[37]	RS	H	44	14.2 ± 2.4 (6–18)	18%	Chêneau	ARF PRF LLF PBF VBF PSF	X-ray; 2 months	Coronal and sagittal rotation of the pelvis can influence the initial in-brace correction in a Chêneau brace in patients with lumbar IS. The initial in-brace correction was negatively correlated with ARF (B=-0.385) and PRF (B= -0.387). The LLF, PBF, VBF and PSF were not related to initial in-brace correction.
Lang et al. 2019[29]	RS	H	119	12.6 ± 1.16 (10–15)	15%	Gensingen	-C-DAR -Curve type -Pre-brace Cobb angle -Age -Gender -Weight -Height -BMI -Risser stage -Menarche status	X-ray; <6 weeks.	-A strong negative correlation was observed between coronal deformity angular ratio (C-DAR) and initial in-brace correction in a Gensingen brace (Pearson or Spearman correlation efficient(r)=-0.69, P<0.01). C-DAR can be applied to estimate initial in-brace correction. -A negative correlation was found between initial in-brace correction and pre-brace major curve Cobb angle (r=-0.29, P<0.01). -No significant correlation was established between initial in-brace correction and patient age (r=0.12, P=0.90), gender (r=0.11, P=0.22), weight (r=0.17, P=0.08), height (r=0.15, P=0.13), BMI (r=0.08, P=0.42), menarche status (r=-0.11, P=0.30), Risser stage (r=-0.06, P=0.51), and curve (thoracic vs. (thoraco)lumbar curves, P=0.79).

Lang et al. 2019[26]†	RS	L	112	12.6 ± 1.2 (10-15)	16%	Gensingen	-Curve type -Pre-brace total, major and minor curve Cobb angle -Age -Gender -Weight -Height -BMI -RVAD -RVA-cx -RVA-cv -Risser stage -Menarche status -LPR -Spinal imbalance	X-ray; CD	-A negative correlation was found between initial in-brace correction in a Gensingen brace and pre-brace total (>55 degrees, Pearson or Spearman correlation efficient(r)=-0.39, P<0.01), major (>30 degrees, r=-0.32, P<0.01) and minor curve Cobb angle (r=-0.23, P=0.02), and LPR (r=-0.29, P=0.03). -Spinal coronal (P=0.01) or sagittal imbalance (P<0.01) can also significantly decrease initial in-brace correction. -No significant correlation was established between initial in-brace correction and patient age (r=0.03, P=0.79), weight (r=0.15, P=0.14), height (r=0.11, P=0.27), BMI (r=0.09, P=0.38), menarche status (P=0.25), gender (P=0.25), Risser stage (P=0.76), curve type (thoracic vs. (thoraco)lumbar curves, P=0.76), RVA-cx (r=-0.13, P=0.36), RVA-cv (r=-0.13, P=0.34) or RVAD (r=0.02, P=0.87).
Boisvert et al. 2008[13]	RS	L	39	NA	NA	Boston	Severity of scoliotic curve	3D reconstruction from biplanar radiographs. <1 day	Severe scoliotic curves in the lower-thoracic segment of the spine had larger corrections in a Boston brace than mild cases which led to larger variabilities.
Chu et al. 2006[10]	PS	L	14	14 ± 1.0 (12 – 15)	0%	TLSO	Different recumbent positions (supine, prone, right and left decubitus)	MRI; <1 day	The largest in-brace correction in a TLSO was observed in the prone position (18% correction in Cobb angle), followed by supine (15%), left decubitus (12%) and right decubitus position (11%).
Bulthuis et al. 2008[16]	PS	L	63	11.3 ± 3.1	10%	TriaC	Amount of force applied in TriaC-brace	X-ray; 4 months	An increase in the continuous corrective force applied in a TriaC-brace resulted in improved initial in-brace corrections.
Cobetto et al. 2016[19]	RCT	L	40	13.1 (10-16)	13%	TLSO	Braced designed with CAD/CAM-FEM method	EOS radiograph; NA	Significant better initial in-brace thoracic Cobb angle correction (P=0.02) and similar/slightly better lumbar curve correction in a TLSO can be obtained with the addition of a FEM simulation platform to CAD/CAM compared to CAD/CAM alone, with the additional advantages of 50 % thinner braces with 20 % less covering body surface.
D'Amato et al. 2001[20]	PS	L	102	NA (10-16.5)	0%	Providence	-Curve flexibility -Risser stage -Curve apex -Curve pattern	X-ray; NA	The Providence brace provides an average initial in-brace Cobb angle correction measured on a supine radiograph of 96% for major curves and 98% for minor curves. The univariate analysis of success (>75% in-brace correction) showed that more flexible curves (P=0.01), Risser 2 compared to Risser 0-1 (P=0.05), and curve apex below T8 (P=0.03) resulted in a higher success rate (78% success versus 43%, P=0.01), The average percentage of initial in-brace correction for each curve type was 94% for thoracic curves, 111% for thoracolumbar curves, 103% for lumbar curves, and 90% and 91%, respectively, for both curves of a

									double curve pattern.
Jarvis et al. 2008[24]	RS	L	23	8.3 years (5.5–9.9)	30%	Charleston	Curve type	X-ray; 3 weeks	A difference in initial in-brace correction (measured in supine position) was found for different curve types in patients with juvenile IS wearing a Charleston Bending Brace. Patients with a single major curve (9 right thoracic and 1 left thoracolumbar) had an initial in-brace correction of 94% (69%–148%). In the 12 double major curves and the 1 triple curve, initial in-brace correction was 76% (0%–123%). Of the 12 double major curves, in-brace correction was 85% (59%– 123%) for the major curves and only 42% (0%–68%) for the secondary curves.
Van den Hout et al. 2002[31]	PS	L	16	13.7 (8–17)	13%	Boston	Compressive force over brace pad	X-ray; 6.5 months	No correlation between magnitude of the mean compressive force over the thoracic (r=0.5) or lumbar brace pad (r=0.3) and degree of in-brace correction of the major curve in a Boston brace was found.
Wong et al. 2005[32]	PS	L	40	12.6 (10 - 14)	0%	NA	Braced designed with CAD/CAM method	X-ray; NA	No significant difference on initial in-brace Cobb angle correction (P=0.12) and apical vertebral rotation correction (P=0.64) was found between the spinal orthoses designed with CAD/CAM and the conventional manual method.
Sankar et al. 2007[28]	PS	L	10	8.9	NA	TLSO	Braced designed with CAD/CAM method	X-ray; 3 weeks	No significant difference on initial in-brace Cobb angle correction was found between the TLSO designed with CAD/CAM (51%) and the plaster molded TSLO (44%), P=0.46).
Desbiens-Blais et al. 2012[21]	PS	L	6	NA (11-13)	0%	TLSO	Braced designed with CAD/CAM-FEM method	EOS radiograph; <1 day	No significant difference on initial in-brace Cobb angle correction was established between the NewBrace designed with CAD/CAM and FEM simulation and the standard TSLO fabricated using the conventional plaster-cast technique (P=0.1 and P=0.5 for main thoracic and thoracolumbar/ lumbar curves, respectively).
Cobetto et al. 2014[22]	PS	L	15	NA (11-14)	0%	TLSO	Braced designed with CAD/CAM-FEM method	EOS radiograph; NA	No significant difference on initial in-brace Cobb angle correction was found between the NewBrace designed with CAD/CAM and FEM simulation and the standard TSLO Boston brace-type fabricated using a plaster-cast method.
Al-aubaidi et al. 2013[15]	PS	L	24	12.8	0%	Providence	In- vs. outpatient protocols at the initiation phase of brace treatment	X-ray; 2 weeks	No significant difference on primary in-brace correction was established between in hospitalization and outpatient clinic protocols, at the initiation phase of brace treatment with a Providence night time only brace.
Goodbody et al. 2016[14]	RS	L	182	12.5 ±1.4 (10-16)	14%	TLSO	BMI	X-ray; NA	-Patients with a high BMI (BMI >85th percentile) were significantly more likely to have poor in-brace correction (≤45% correction) in a TLSO, compared to patients with a mid-BMI (BMI 20th – 85th percentile) (P=0.02). The odds ratio for poor in-brace correction between these two groups was 5.5 (P=0.01). -Also patients with a low BMI (BMI <20th percentile) showed a trend

									towards poorer in-brace curve correction compared to the mid-BMI patients (P=0.21). The odds ratio for poor in-brace correction between these two groups was 1.8 (P=0.17).
Babaee et al. 2020[33]	RS	L	75	6.94 ± 1.86	24%	Milwaukee	Curve type	X-ray; 4-6 months	Better best in-brace Cobb angle correction in a Milwaukee brace or TLSO was observed in juvenile IS patients with Lenke type I (55%), Lenke type II (59%) and Lenke type V (62%) curves, compared to Lenke type III (41%) curves.
Li et al. 2014[11]	PS	L	9	12.9	0%	NA	Time in brace before assessment of initial in-brace correction	Clinical ultrasound; 1 day	A time lag between brace application and its effect on scoliotic curve was observed. The spinal response to brace application or removal seemed to plateau after approximately 120 minutes.
Weiss et al. 2007[27]	PS	L	81	12.9 ± 1.9	NA	Cheneau light	-Curve type -Pre-brace Cobb angle -Age -Risser stage	X-ray; 6 weeks	-A significant negative correlation was found between initial in-brace correction in a “Cheneau light” brace and age (r=-0.24, P=0.01), Risser stage (r=-0.29, P=0.01), and pre-brace Cobb angle (r=-0.43, P<0.01). -Higher initial in brace correction was achieved in lumbar and thoracolumbar curves (62%), compared to thoracic (36%) and double major curve pattern (50%).
Aubin et al. 1997[12]	PS	L	36	12.5 ±1.7	11%	Boston	-Transverse displacements of the rib cage -Derotation forces on rib hump -Anterior displacements of the rib cage at apical level	3D reconstruction from two radiographs; 1-6 months.	-Translations generated by the Boston brace system on the thorax generally are statistically and linearly related to corresponding corrections of the spine at the apical level. -Derotation forces at the apex of the rib hump are limited and do not allow the reduction of axial rotation (Pearson correlation(r)=0.12), but are correlated with the reduction of spine offset in the frontal plane (r=0.43). -A tendency was found that anterior displacements of the rib cage at apical level is accompanied by an increase of the spinal thoracic curve (r=-0.41, P=0.01). Clinicians should try to reduce anterior displacements of the rib cage by decreasing or reequilibrating orthotic loads applied on the posterior rib hump.
Çhan et al. 2014[17]	PS	L	42	12.6 ± 1.0 (11-15)	0%	TLSO (HK brace)	-Curve pattern -Brace compliance	X-ray; 4-6 months	-Patients in the major thoracolumbar curvature group were found to have a significantly increased in-brace correction in a TSLO, named the Hong Kong brace, compared to patients in the major thoracic curvature group (P=0.002). It was predicted that patients with a thoracic curve pattern would have 5.4 less in difference of Cobb angle compared to patients with a thoracolumbar curve pattern. -No significant difference on in-brace correction (below 40% and 40% or above) was detected between three groups of different hours of brace wear (0–8 hours, 9–16 hours, and 17–23 hours). A significant correlation was found between subjective compliance and the objective compliance (wearing hours recorded by the orthosis monitoring system).

4

*Time frame between out-of-brace images or start brace wear and in-brace images for the determination of in-brace correction.

†This study probably included also patients from Lang et al. 2019[29]

Abbreviations: QA, quality assesment (High (H) or low quality (L) study according to QA, see table 2); N, number of patients; NA, not available; PS, prospective study; RS retrospective study; RCT, randomized and controlled trial; BMI, body mass index; vs.; versus; RSO, rigid spinal orthosis; TLSO, thoracic lumbar sacral orthosis; RSC, Rigo System Chêneau brace; HK brace, Hong Kong brace; EOS, a low-dose digital radiography system; AIS, adolescent idiopathic scoliosis; FEM, finite element models; CAD/CAM, Computer-aided design and manufacturing systems; LPR, lumbo-pelvic ratio; RVAD, rib vertebral angle difference; RVA-cx, rib vertebral angle - convex side, RVA-cv, rib vertebral angle - concave side; C-DAR, coronal deformity angular ratio; SLBR, suspine lateral bending radiographs; MT, main thoracic; TL/L, thoraco-lumbar/lumbar; TK, thoracic kyphosis; LL, lumbar lordosis; ARF, apical rotate factor; PCPR, pelvic coronal plane rotation; AVR, apical vertebral rotation; PRF, pelvic rotate factor; PT, pelvic tilt; PI, pelvic incidence; LLF, lumber lordosis factor; PBF; coronal balance factor, VBF; vertical balance factor, PSF; pelvic symmetry factor.

Supplementary data 2. Quality assessment

First author, year of publication	Item 1A	1B	2	3	4	5	6	7	8	9	Number of items scored with 'yes'
Cheung et al. 2018[18]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	CD	7
He et al. 2017[23]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	CD	7
Labelle et al. 2007[25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	CD	7
Hedayati et al. 2018[35]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	8
Karam et al. 2019[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	CD	8
Ohrt-Nissen et al. 2016[30]	Yes	Yes	No	Yes	Yes	CD	Yes	Yes	Yes	Yes	8
Guy et al. 2021[34]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	8
Li, 2020[37]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9
Lang et al. 2019[29]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	CD	8
Lang et al. 2019[26]	Yes	Yes	Yes	Yes	No	CD	Yes	Yes	CD	CD	6
Boisvert et al. 2008[13]	No	No	No	No	No	Yes	No	CD	CD	CD	1
Chu et al. 2006[10]	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	CD	6
Bulthuis et al. 2008[16]	No	No	Yes	Yes	Yes	No	No	Yes	No	CD	4
Cobetto et al. 2016[19]	Yes	Yes	No	Yes	No	CD	Yes	Yes	CD	CD	5
d'Amato et al. 2001[20]	No	No	No	Yes	No	CD	Yes	Yes	No	Yes	4
Jarvis et al. 2008[24]	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes	5
Van den Hout et al. 2002[31]	Yes	Yes	No	No	No	No	Yes	Yes	No	CD	4
Wong et al. 2005[32]	Yes	Yes	No	Yes	No	CD	Yes	Yes	No	CD	5
Sanker et al. 2007[28]	Yes	Yes	No	No	No	Yes	Yes	Yes	No	CD	5
Desbiens-Blais et al. 2012[21]	No	No	No	No	No	Yes	Yes	Yes	No	CD	3
Cobetto et al. 2014[22]	No	No	No	No	No	CD	Yes	Yes	No	CD	2
Al-Aubaidi et al. 2013[15]	No	Yes	Yes	Yes	No	No	No	Yes	CD	CD	4
Goodbody et al. 2016[14]	Yes	Yes	Yes	Yes	No	CD	Yes	Yes	No	No	6
Babaee et al. 2020[33]	No	No	Yes	Yes	No	No	No	Yes	No	NO	3
Li et al. 2014[11]	Yes	Yes	No	Yes	No	Yes	Yes	No	No	CD	5
Weiss et al. 2007[27]	No	No	No	No	No	Yes	No	Yes	No	CD	2
Aubin et al. 1997[12]	Yes	No	Yes	No	No	No	Yes	Yes	No	CD	4
Chan et al. 2014[17]	No	No	No	Yes	No	No	No	Yes	No	No	2

For the description of items 1-9 see table 2
Abbreviations: CD, cannot determine

CHAPTER 5

Are torso asymmetry and torso displacements in a computer brace model associated with initial in-brace correction in adolescent idiopathic scoliosis?

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BMC musculoskeletal disorders. 2023 May 8;24(1):361

Abstract

Background: Lack of initial in-brace correction is strongly predictive for brace treatment failure in adolescent idiopathic scoliosis (AIS) patients. Computer-aided design (CAD) technology could be useful in quantifying the trunk in 3D and brace characteristics in order to further investigate the effect of brace modifications on initial in-brace correction and subsequently long-term brace treatment success. The purpose of this pilot study was to identify parameters obtained from 3D surface scans which influence the initial in-brace correction (IBC) in a Boston brace in patients with AIS.

Methods: 25 AIS patients receiving a CAD-based Boston brace were included in this pilot study consisting of 11 patients with Lenke classification type 1 and 14 with type 5 curves. The degree of torso asymmetry and segmental peak positive and negative torso displacements were analyzed with the use of patients' 3D surface scans and brace models for potential correlations with IBC.

Results: The mean IBC of the major curve on AP view was 15.9% (SD=9.1%) for the Lenke type 1 curves, and 20.1% (SD=13.9%) for the type 5 curves. The degree of torso asymmetry was weakly correlated with patient's pre-brace major curve Cobb angle and negligible correlated with major curve IBC. Mostly weak or negligible correlations were observed between IBC and the twelve segmental peak displacements for both Lenke type 1 and 5 curves.

Conclusion: Based on the results of this pilot study, the degree of torso asymmetry and segmental peak torso displacements in the brace model alone are not clearly associated with IBC.

Introduction

bracing of adolescent idiopathic scoliosis (AIS) is effective to stop progression of the curve in 72% of the patients[1]. The Boston brace is a widely used brace system, which consists of a prefabricated symmetric module that is customized to fit an individual patient's body shape and spinal curvature[2, 3]. Unfortunately, brace treatment is not successful in every AIS patient. Apart from brace compliance, strong evidence has been reported for lack of initial in-brace correction as a predictive factor for brace treatment failure[4].

Curve type and curve flexibility are the best proven factors influencing this initial in-brace correction, but these patient factors cannot be influenced by the orthotist[5]. Translations generated by the brace on the thorax generally are statistically and linearly related to corresponding corrections of the spine, and a positive correlation has been reported between the correction of the lumbar scoliosis and correction of the lumbar lordosis[6, 7]. To influence these translations generated by the brace, computer-aided design and manufacturing systems (CAD/CAM) combined with or without finite element models (FEM) simulation have been applied. So far, theydo not significantly improve initial in-brace correction compared to a conventional plaster-cast method[5, 8-11]. However, these CAD technologies could be useful in quantifying the trunk in 3D and brace characteristics in order to further investigate the effect of brace modifications on initial in-brace correction and subsequently long-term brace treatment success. The purpose of this pilot study was to identify parameters obtained from 3D surface scans which influence the initial in-brace correction (IBC) in a Boston brace in patients with AIS. The degree of torso asymmetry (i) and segmental peak positive and negative torso displacements (ii) will be analyzed with the use of patients' 3D surface scans and brace models for potential correlations with IBC.

Methods

Patients

This retrospective pilot study was approved by the Medical Ethical Review Board (RR-number: 201800846). Inclusion criteria were: AIS patients aged between 10 and 17 years (i), with a pre-brace Lenke classification type 1 or 5 curve (ii), and a pre-brace Cobb angle of the major curve of 20 degrees or more (iii), undergoing Boston brace treatment manufactured with CAD (iv)[12]. Patients with non-idiopathic scoliosis or previous spine operations were excluded. All eligible patients, retrieved from a database of Boston brace users, were approached for study participation by mail, telephone or at the outpatient clinics. The first 25 patients who gave their informed consent were included in this pilot study.

Method of measurements

Pre-brace and in-brace standing biplanar low-dose radiographs of the spine were made using EOS®imaging, Paris, France[13, 14]. Two independent observers (CP and CF) determined the Lenke classification of the scoliosis deformities and separately measured the major curve Cobb angle on the anteroposterior (AP) and lateral view[12]. When the difference in Cobb angle between the observers was exceeding 5 degrees, a consensus meeting was planned. In the results, the data are presented as the mean of both observers.

The brace manufacturing process consisted of 3D torso scans from which a virtual brace model was designed. These brace 3D models have been prepared by the orthotist at the time of brace manufacturing. This process included virtual reshaping of the torso scan towards the desired torso, which was then milled out of a foam block, forming a mold for the final brace. For this study all 3D surface scans and brace models of included patients were obtained from the orthotist and analysed by a technical physician from our point-of-care 3D lab (PP), who were both blinded for initial in-brace correction.

First the asymmetry index was determined for all the torso and brace models. Due to the lack of available standardized methods to assess the torso asymmetry, this study's method was based on a variety of methods for assessing facial asymmetry[15]. The surface models were imported into 3-matic v12 (Materialise, Belgium, Leuven) (figure 1A). First, manual positioning of mirroring planes was performed, the models were then mirrored across these planes. Next, the mirrored models were registered to the original models using the in-software iterative closest point (ICP) algorithm (figure 1B). The top and bottom of these models were then trimmed in order to obtain equal length (figure 1C). Finally, the volume enclosed between the mirrored model and the original model was measured and divided by the total volume of the original model, providing us with the asymmetry percentage (figure 1D). The asymmetry percentage was calculated for the torso as well as the brace models.

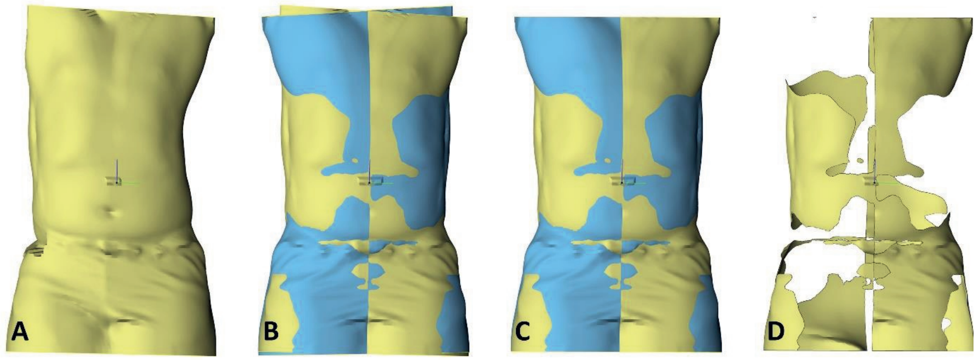

Figure 1: Symmetry analysis showing, A) the torso scan in yellow, B) registered mirrored torso scan in blue, C) the trimmed to equal length, and D) the volume between both surfaces.

The second parameter was based on surface-to-surface distance measurements between the torso scan and the brace model. The surface-to-surface analysis in 3-matic was used to measure the closest distance of each surface point on the torso surface to the nearest neighbouring point on the brace model. At the areas where the brace model was situated ‘inside’ the torso this resulted in a positive value (or red color), and at places where the brace was situated ‘outside’ the torso the algorithm provided with a negative value or a blue color (figure 2). I.e. a positive value corresponds to areas where the brace is *pressed* against the torso (pressure zone), and a negative value corresponds with areas where the torso could move away from the brace (expansion zone). For the final analysis the analysis model is divided into 12 segments. Two cross sectional planes are created by 2 planes in the z-direction, creating an upper, middle and lower segment, which are equally divided. A coronal midplane and a sagittal midline then divide the torso into 12 segments (Figure 3).

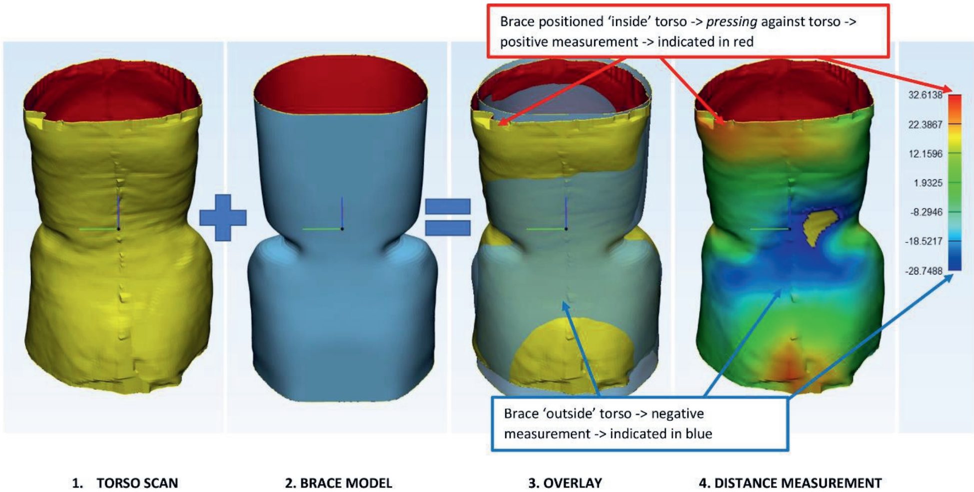

Figure 2: Surface-to-surface measurements. The torso scans and brace model are properly aligned by the orthotist. From each point on the torso scan the distance towards the brace model is measured using an algorithm. At the surface areas where the brace provides space to the torso this results in negative values and a blue color (expansion zone). For the red area there is an opposite effect; here the brace is *pressing* against the torso (pressure zone).

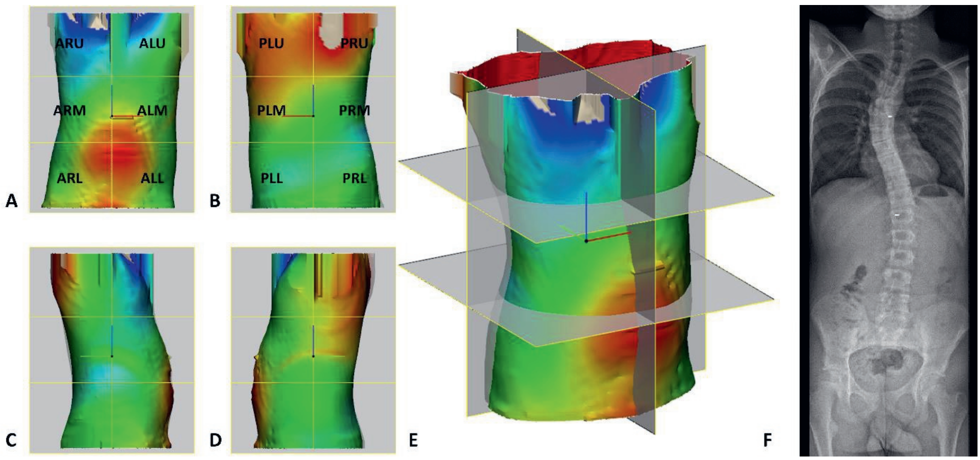

Figure 3: Surface-to-surface measurements (A-E) and EOS radiograph (F) of a typical case, in A) anterior, B) posterior, C) right, D) left, E) perspective view. Initial in-brace correction=9.6%.
Abbreviations:ALU, anterior left upper segment, ARU, anterior right upper segment; ALM, anterior left midsegment; ARM, anterior right midsegment; ALL, anterior left lower segment; ARL, anterior right lower segment; PLU, posterior left upper segment, PRU, posterior right upper segment; PLM, posterior left midsegment; PRM, posterior right midsegment; PLL, posterior left lower segment; PRL, posterior right lower segment.

Statistical analyses

Spearman's rho correlation coefficients were calculated to determine the correlation between the torso asymmetry index and pre-brace major curve Cobb angle and initial in-brace correction (i), and correlations between segmental peak positive and negative displacements and initial in-brace correction separately for Lenke 1 and 5 curves.A Spearman's rho of 0.90-1.00 indicates a very strong correlation, a Spearman's rho of 0.70-0.89 indicates a strong correlation, 0.50-0.69 moderate, 0.26-0.49 weak, and ≤0.25 represents little if any correlation[16-18].IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Patient inclusion and characteristics

Twenty-five patients with a mean age of 14 years (SD=1.5) at start Boston brace treatment were included in this pilot study (Table 1). Eleven patients had a type 1 curve and 14 patients a type 5 curve according to the Lenke classification. All type 1 curves were thoracic right-convex and all type 5 curves were lumbar left-convex. Sixteen patients (64%) were female. The mean pre-brace Cobb angle of the major curve were 38.4 degrees (SD=14.8) and 30.5 degrees (SD=5.8) for the type 1 and type 5 curve, respectively. The mean initial in-brace correction of the major curve was 15.9% (SD=9.1%) for the type 1 curves, and 20.1% (SD=13.9%) for the type 5 curves. All initial in-brace corrections were the result of the CAD correction without additional padding. If necessary, further improved with adjustment of the brace pads were done by the orthotist after the first in-brace radiograph. These additional corrections by pads were not included in the measurements. The mean time interval between pre-brace and in-brace radiographic follow-up images was 3.3 months (SD=1.5). Six patients (26%) of which 5 patients (80%) with a Lenke type 1 curve had brace treatment failure, which was defined as indication for surgery.

Table 1: Patient characteristics

Criterion		Study population
Gender, female*		16 (64%)
Age at start Boston brace treatment		14.0 ± 1.5
Brace initiation before menarche*		6 (38%)
Pre-brace Lenke classification*[12]		
Lenke 1		11 (44%)
Lenke 5		14 (56%)
Pre-brace Nash Moe classification at major curve apex*[24]		
Nash moe 0		1 (4%)
Nash moe 1		6 (24%)
Nash moe 2-3		18 (72%)
Brace treatment failure*‡		6 (26%)
	Lenke 1 (n=11)†	**Lenke 5 (n=14)†**
Pre-brace major curve CA on AP view	38.4± 14.8	30.5± 5.8
Initial in-brace correction major curve on AP view in CA degrees	6.2± 3.7	6.0± 3.7
Initial in-brace correction major curve on AP view in %	15.9± 9.1	20.1± 13.9
Pre-brace major curve CA on lateral view	21.2 ± 15.0	48.3 ± 11.9
Initial in-brace correction major curve on lateral view in CA degrees	4.5 ± 5.8	7.0 ± 6.9
Initial in-brace correction major curve on lateral view in %	5.1 ± 81.9	13.7 ± 14.4

**Values are presented as number (percentage)*
†Values are presented as mean ± standard deviation
†Brace treatment failure was defined as indication for surgery
Abbreviations: AP, anteroposterior; CA, Cobb angle; n, number of patients with Lenke 1 or Lenke 5 curve; SD, standard deviation.

Torso asymmetry, pre-brace Cobb angle and in-brace correction

The mean torso asymmetry index was 5.6% (SD=1.6) for patients with type 1 curves, and 3.9% (SD=1.3) for type 5 curves (Table 2). A weak positive correlation was observed between patients' torso asymmetry index and pre-brace major curve CA on AP view for both type 1 and 5 curves (Spearman's rho=0.29 and 0.33, respectively). Little or negligible negative correlation was found between patient's torso asymmetry index and initial in-brace correction on AP view (Spearman's rho=-0.08 for Lenke type 1 curves, and Spearman's rho=-0.14 for type 5 curves, see table 2).

Table 2: Torso asymmetry

Criterion	Lenke 1 (n=11) Mean ± SD	Lenke 5 (n=14) Mean ± SD
Torso asymmetry index in %	5.64 ± 1.60	3.93 ± 1.30
Brace asymmetry index in %	0.18 ± 0.36	0.08 ± 0.11
Correlation with torso asymmetry index	**Spearman's rho**	**Spearman's rho**
Pre-brace major curve CA on AP view	0.29	0.33
Initial in-brace correction major curve on AP view	-0.08	-0.14
Pre-brace major curve CA on lateral view	-0.29	-0.17
Initial in-brace correction major curve on lateral view	-0.37	-0.06

Abbreviations: AP, anteroposterior; CA, Cobb angle; n, number of patients with Lenke 1 or Lenke 5 curve; SD, standard deviation.

Peak torso displacement and in-brace correction

For the type 1 curves a strong negative correlation was observed between the peak negative torso displacement in the anterior right midsegment (ARM) and major curve IBC (Spearman's rho=-0.72, see table 3). Also, a moderate correlation was observed between the peak positive displacement in the posterior left midsegment (PLM) and IBC (Spearman's rho=0.64), and a moderate negative correlation was observed between the peak positive displacement in the anterior right upper segment (ARU) and IBC (Spearman's rho=-0.51), and the peak negative displacement in the posterior right midsegment (PRM) and IBC (Spearman's rho=-0.55). Weak or little if any correlation was observed between the other segmental peak positive and negative displacements and IBC (Spearman's rho<0.50, see table 3).

Table 3: Correlations between segmental peak positive and negative torso displacements and initial in-brace correction in Lenke 1 curves.

Correlation with IBC	Little if any correlation rho≤0.25	Weak correlation rho=0.26-0.49	Moderate correlation rho=0.50-0.69	Strong correlation rho= 0.70-0.89
<u>Peak positive torso displacement</u>				
ALU		-0.43		
ARU			-0.51	
ALM		0.48		
ARM	0.16			
ALL	-0.21			
ARL		-0.26		
PLU		0.47		
PRU		0.33		
PLM			0.64	
PRM		-0.27		
PLL	0.08			
PRL		0.32		
<u>Peak negative torso displacement</u>				
ALU		-0.32		
ARU	-0.10			
ALM		0.28		
ARM				-0.72
ALL	-0.07			
ARL	0.13			
PLU	0.09			
PRU	-0.05			
PLM	-0.13			
PRM			-0.55	
PLL	0.09			
PRL	-0.01			

Abbreviations: IBC, initial in-brace correction; rho, Spearman's rho; ALU, anterior left upper segment, ARU, anterior right upper segment; ALM, anterior left midsegment; ARM, anterior right midsegment; ALL, anterior left lower segment; ARL, anterior right lower segment; PLU, posterior left upper segment, PRU, posterior right upper segment; PLM, posterior left midsegment; PRM, posterior right midsegment; PLL, posterior left lower segment; PRL, posterior right lower segment.

For type 5 curves, only weak or negligible correlations were found between the peak positive displacements in the twelve segments and IBC (Table 4). Regarding the peak negative displacements, a strong negative correlation was observed between this displacement in the PLM segment and IBC (Spearman's rho=-0.85). Also a moderate negative correlation was observed between the peak negative displacement in the posterior left upper segment (PLU) and IBC (Spearman's rho=-0.54, see table 4).

Table 4: Correlations between segmental peak positive and negative torso displacements and initial in-brace correction in Lenke 5 curves.

Correlation with IBC	Little if any correlation rho≤0.25	Weak correlation rho=0.26-0.49	Moderate correlation rho=0.50-0.69	Strong correlation rho= 0.70-0.89
Peak positive torso displacement				
ALU	-0.01			
ARU	-0.04			
ALM	0.04			
ARM		0.26		
ALL	-0.05			
ARL	-0.24			
PLU	-0.13			
PRU		-0.31		
PLM		-0.34		
PRM	-0.11			
PLL	0.07			
PRL	0.21			
Peak negative torso displacement				
ALU	-0.11			
ARU	0.01			
ALM		0.26		
ARM	0.16			
ALL		-0.27		
ARL		-0.49		
PLU			-0.54	
PRU	0.04			
PLM				-0.85
PRM	-0.23			
PLL		-0.37		
PRL	-0.25			

Abbreviations: IBC, initial in-brace correction; rho, Spearman's rho; ALU, anterior left upper segment, ARU, anterior right upper segment; ALM, anterior left midsegment; ARM, anterior right midsegment; ALL, anterior left lower segment; ARL, anterior right lower segment; PLU, posterior left upper segment, PRU, posterior right upper segment; PLM, posterior left midsegment; PRM, posterior right midsegment; PLL, posterior left lower segment; PRL, posterior right lower segment.

Correlations between segmental peak positive and negative displacement and IBC on lateral radiographs for both type 1 and 5 curves are presented in the supplementary data table 1 and 2. Besides a moderate negative correlation between the peak positive displacement in the anterior left lower segment (ALL) and major curve IBC on lateral radiographs (Spearman's rho=-0.54), and a moderate positive correlation between peak negative displacement in the PLM segment and IBC (Spearman's rho=0.54) in type 1 curves, all correlations between the twelve segmental peak positive and negative displacements and IBC on lateral images were weak or negligiblefor both type 1 and 5 curves (Spearman's rho<0.50).

Discussion

The purpose of this pilot study with CAD/CAM technology was to provide a first impression on the effect of increased or decreased torso asymmetry and segmental peak positive or negative torso displacements on radiographic IBC in patients with AIS. The results of this study suggest that the degree of torso asymmetry correlates weakly with pre-brace major curve Cobb angle on a coronal view for both Lenke type 1 and 5 curves, and does little or negligibly correlate with IBC. Regarding the segmental peak torso displacements, only the peak negative torso displacement in the ARM segment had a strong negative correlation with IBC in type 1 curves (Spearman's rho=-0.72) and the peak negative torso displacement in the PLM segment had a strong negative correlation with IBC (Spearman's rho= -0.85) in type 5 curves. These results indicate that a larger expansion zone in the ARM segment is associated with less IBC in thoracic right-convex Lenke type 1 curves, and that a larger expansion zone in the PLM segment is associated with less IBC in lumbar left-convex Lenke type 5 curves.

In literature, lumbar flexion, transverse forces applied by foam pads according to the 3 or 4 pressure point principle, and total contact fit of the brace are described as mechanisms to achieve curve correction[2, 6].Using this pressure point principle, one would expect that curve correction in type 1 curves are associated to peak positive displacements in the posterior right upper segment (PRU) and anterior left upper segment (ALU), and in type 5 curves to peak positive displacements in the PLM and ARM segments. However, only weak (PRU, ARM) or weak negative correlation (ALU, PLM) with IBC were observed for these segments. On the other hand, the observed strong negative correlation between the peak negative torso displacement in the PLM segment and IBC in lumbar left-convex Lenke type 5 curves (Spearman's rho= -0.85)could be explained by the expectation that the PLM segment should be a "pressure zone" and not an "expansion zone" according this pressure point principle. For the peak negative displacements (expansion zone), it was hypothesized that IBC was associated with peak negative displacements in the PLU and ARU for type 1 curves, and in the anterior left midsegment (ALM) and PRM segments for the type 5 curves. Also for these segments only weak (ALM) or negligible (PLU, ARU, PRM) correlation were seen with IBC. A possible explanation for the weak and negligible correlations is that peak positive displacement does not correlate with amount of applied *pressure.* A comparable amount of displacement directly applied on bones, for instance, would result in a larger spinal torso displacement compared to the same displacement on fat tissue. So far, there is insufficient evidence in literature that the magnitude of the corrective force over brace pads is correlated to the degree of radiographic

IBC[19-22]. To obtain a better understanding of the correction mechanisms of the brace, future studies should focus on combined analysis of the peak positive displacement of the brace and pressure forces applied to the torso.

Clinical implications

Identifying parameters obtained from 3D surface scans which influence IBC would be very useful in daily practice in order to investigate the effect of brace modifications on IBC and subsequently long-term brace treatment success. Based on the results of this pilot study, the degree of torso asymmetry and segmental peak torso displacements in the brace alone are not helpful in predicting IBC. It is, however, possible that when segmental peak torso displacements in-brace are combined with other factors such as pad pressure, they could be of added value in predicting IBC and/or improving brace comfort. Future studies on CAD brace related factors that influences IBC should therefore include both quantifiable parameters obtained from 3D surface scans and brace models, and pad pressure parameters in-brace obtained with electronic pressure sensors[19, 22]. In these future studies, bending radiographs before brace treatment would be an interesting additional parameter to assess besides radiographic initial in-brace correction because of the strong association between curve flexibility and initial in-brace correction[5].

Limitations

When interpreting the results of this study a few limitations should be considered. This was a pilot study with a small sample size and a potential selection bias since the first 25 patients who gave their informed consent were included in this study. The mean initial in-brace correction of the studied group was relatively small compared to literature[23]. Once fabricated, these in-brace correction were further improved by applications of pressure pads in the brace. Therefore, these corrections only represent the CAD part of the correction. For this study it was, however, more interesting to observe the direct results of the braces fabricated with CAD technology and not with manual adjustments by the orthotist. The absence of manual adjustments by the orthotist could therefore be the reason for this relatively small in-brace correction. A limitation of dividing the 3D surface scan in twelve equally divided parts is that peak pressure points of the brace on curve apices and therefore possibly also peak displacement points might fall in different segments as a result of the variety of curve deformities. But on the other hand, dividing the 3D surface scan in anatomical sections would bring diversity in segment sizes, would be labour-intensive and possibly affect reproducibility since it must be performed manually.

Conclusion

In conclusion, this pilot study shows that the degree of torso asymmetry in AIS patients with Lenke type 1 and 5 curves is weakly correlated with patient's pre-brace major curve Cobb angle on a coronal radiograph and negligible correlated with major curve IBC. Besides a strong negative correlation between peak negative torso displacement in the ARM segment and IBC in thoracic right-convex Lenke type 1 curves, and a strong negative correlation between the peak negative torso displacement in the PLM segment and IBC in lumbar left-convex type 5 curves, only some moderate, and mostly weak or negligible correlations were observed between IBC and the other segmental peak displacements for both Lenke type 1 and 5 curves. A possible explanation for the strong negative correlation between peak negative torso displacement in the PLM segment and IBC in type 5 curves is the expectation that the PLM segment should be a "pressure zone" and not an "expansion zone" according the pressure point principle.

The general results of this study indicate that the degree of torso asymmetry and segmental peak torso displacements in the brace model alone are not clearly associated with IBC. Therefore, it is highly probable that other brace related factors such as pad pressure parameters contribute to better prediction and further improvement of IBC.

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Supplementary data

Supplementary data 1: Correlations between segmental peak positive and negative torso displacements and initial in-brace correctionon lateral radiographs in Lenke 1 curves.

Correlation with IBC	Little if any correlation rho≤0.25	Weak correlation rho=0.26-0.49	Moderate correlation rho=0.50-0.69	Strong correlation rho= 0.70-0.89
Peak positive torso displacement				
ALU	-0.18			
ARU	-0.04			
ALM		-0.27		
ARM	-0.08			
ALL			-0.54	
ARL		-0.48		
PLU	-0.24			
PRU	0.04			
PLM	0.24			
PRM		-0.36		
PLL	0.16			
PRL	-0.03			
Peak negative torso displacement				
ALU	0.02			
ARU	0.04			
ALM	0.22			
ARM	0.25			
ALL	-0.16			
ARL	0.12			
PLU		0.31		
PRU		0.47		
PLM			0.54	
PRM		0.27		
PLL		0.39		
PRL		0.31		

Abbreviations: IBC, initial in-brace correction; rho, Spearman's rho; ALU, anterior left upper segment, ARU, anterior right upper segment; ALM, anterior left midsegment; ARM, anterior right midsegment; ALL, anterior left lower segment; ARL, anterior right lower segment; PLU, posterior left upper segment, PRU, posterior right upper segment; PLM, posterior left midsegment; PRM, posterior right midsegment; PLL, posterior left lower segment; PRL, posterior right lower segment.

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Supplementary data 2: Correlations between segmental peak positive and negative torso displacements and initial in-brace correctionon lateral radiographs in Lenke 5 curves.

Correlation with IBC	Little if any correlation rho≤0.25	Weak correlation rho=0.26-0.49	Moderate correlation rho=0.50-0.69	Strong correlation rho= 0.70-0.89
Peak positive torso displacement				
ALU	-0.21			
ARU	0.11			
ALM	-0.19			
ARM		-0.32		
ALL	-0.15			
ARL	-0.06			
PLU	0.10			
PRU	-0.20			
PLM	-0.20			
PRM	0.06			
PLL		0.33		
PRL	0.16			
Peak negative torso displacement				
ALU	0.02			
ARU	0.06			
ALM	-0.13			
ARM	0.09			
ALL	-0.12			
ARL	0.03			
PLU	-0.20			
PRU		-0.42		
PLM	0.15			
PRM	0.22			
PLL	-0.09			
PRL	-0.20			

Abbreviations: IBC, initial in-brace correction; rho, Spearman's rho; ALU, anterior left upper segment, ARU, anterior right upper segment; ALM, anterior left midsegment; ARM, anterior right midsegment; ALL, anterior left lower segment; ARL, anterior right lower segment; PLU, posterior left upper segment, PRU, posterior right upper segment; PLM, posterior left midsegment; PRM, posterior right midsegment; PLL, posterior left lower segment; PRL, posterior right lower segment.

CHAPTER 6

In-brace versus out-of-brace protocol for radiographic follow-up of patients with idiopathic scoliosis

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Abstract

Purpose: The purpose of this retrospective study was to compare two standardized protocols for radiological follow-up (in-brace versus out-of-brace radiographs) to study the rate of curve progression over time in surgical treated idiopathic scoliosis (IS) patients after failed brace treatment. In-brace radiographs have the advantage that proper fit of the brace and in-brace correction can be evaluated. However detection of progression might theoretically be more difficult.

Methods: Fifty-one IS patients that underwent surgical treatment after failed brace treatment were included. For 25 patients, follow-up radiographs were taken in-brace. For the other 26 patients, brace treatment was temporarily stopped before out-of-brace follow up radiographs were taken.

Results: Both groups showed significant curve progression compared to baseline after a mean follow up period of 3.4 years. The protocol with in-brace radiographs was non-inferior regarding curve progression rate over time. The estimated monthly Cobb angle progression based on the mixed effect model was 0.5 degrees in both groups. No interaction effect was found for time and patients' baseline Cobb angle (P=0.98) and for time and patients' initial in-brace correction (P=0.32).

Conclusion: The results of this study indicate that with both in-brace and out-of-brace protocols for radiographic follow-up a similar rate of curve progression can be expected over time in IS patients with failed brace treatment.

Introduction

Idiopathic scoliosis (IS) is a common three-dimensional deformity of the spine involving a coronal major curve Cobb angle exceeding 10 degrees and spinal rotation[1]. The prevalence of IS is approximately 3% for children younger than 16 years old, of which ten percent have progressive spinal curves and requires treatment[2, 3]. Severe curves with a Cobb angle exceeding 45-50 degrees have a high risk of progression in adulthood and are therefore often treated surgically with posterior spinal instrumentation and fusion using pedicle screws[4-7]. The best proven non-surgical treatment is rigorous bracing during a number of years of the adolescent growth spurt with the aim of maintaining the curve below 45 degrees. A randomized and preference cohort trial reported a treatment rate success of 72% after bracing, compared to 48% after observation[2]. The success rate of bracing was mainly associated with compliance as there was a significant positive association between hours of brace wear and rate of treatment success[2, 8]. Therefore, early detection of curve progression during brace treatment is important for motivational reasons as the most important positive factor influencing brace compliance is the patient's desire to avoid surgery and to prevent curve progression[9].

To detect curve progression during brace treatment, regular follow-up radiographs are usually made at 6 month intervals[3]. According to the SOSORT bracing protocol, these radiographs should be taken out-of-brace to examine the effectiveness of treatment (level V of evidence)[3]. On the contrary, follow-up with in-brace radiographs has the advantage that proper fit of the brace and in-brace correction can be evaluated. However, it has been assumed that detection of progression might theoretically be more difficult when taking in-brace radiographs, since the curve is partially corrected.

To date, there are no studies that have analyzed these two different radiographic follow-up strategies for the ability to detect progression and the rate of progression. Therefore, this study will compare two standardized protocols for follow-up radiographs (in-brace versus out-of-brace radiographs) from two different scoliosis centers for the ability to detect curve progression over time in idiopathic scoliosis patients with failure of brace treatment.

Methods

Study design

This retrospective study was approved by the Medical Ethical Review Board (RR-number:

201900088) and conducted in two different tertiary care centers for scoliosis. Two standardized protocols for follow-up radiographs (in-brace versus out-of-brace radiographs) were compared. The in-brace group consisted of patients who underwent surgical treatment for idiopathic scoliosis in the first tertiary center after failed brace treatment. The standard protocol of this hospital was to take in-brace follow-up radiographs. The ability to detect curve progression over time on the in-brace radiographs was analyzed, and subsequently compared to the out-of-brace group of surgically treated idiopathic scoliosis patients with failed brace treatment in the second hospital. The standard protocol of the second hospital was to take the first radiograph in the brace to evaluate the in-brace correction and all subsequent follow-up radiographs out-of-brace. Wearing of the brace was discontinued for a minimum of 12 hours before the out-of-brace radiograph was taken. For the out-of-brace radiographs, patients were instructed to take their brace off during dinner, sleep without their brace, and return to the hospital the next morning without wearing the brace. Before taking the radiographs, the time of discontinuation of brace wear was checked.

Patients

Patients from both medical centers were included in this retrospective study according to the following inclusion criteria: They were diagnosed with idiopathic scoliosis below 50 degrees (i), and underwent surgical treatment for scoliosis after failed brace treatment (ii), follow-up of the bracing period with radiographs was for at least 18 months (to be able to detect progression) (iii), and radiographs and patients data were available in the electronic patient records or archives (iv) (Table 1). Patients with non-idiopathic or non-progressive scoliosis, or previous spinal surgery during bracing period were excluded. Scoliosis progression was defined as an increase of Cobb angle of ≥5 degrees during the bracing period[10]. The Boston brace was used for all patients in both centers and the prescribed brace dosage was at least 20 hours per day[11]. Radiographs in other braces than the Boston brace were excluded.

Table 1: Patient inclusion

Inclusion criteria	**Exclusion criteria**
Diagnosed with idiopathic scoliosis	Diagnosed with non-idiopathic scoliosis
Major curve Cobb angle was <50 degrees at study inclusion	Patients with non-progressive scoliosis†
Patients underwent surgical correction after failed brace treatment	Previous spinal surgery during bracing period
Follow-up of the bracing period was with radiographs	Radiographs in other braces than the Boston brace
Follow-up of the bracing period was at least 18 months	
Radiographs and patients data were available	

†*Scoliosis progression was defined as an increase of Cobb angle of ≥5 degrees during the bracing period*

Method of measurements

In the in-brace group, all in-brace radiographs during the bracing period in UMCG were used for analysis. Two independent observers (AH and CP) separately measured the Cobb angle of the major curve of the scoliosis deformity on standing anteroposterior view of each radiograph of the included patients. Data of the in-brace group are presented as the mean of both observers. In the out-of-brace group, the Cobb angles of the major curves on the index radiographs followed by the Cobb angles on all radiographs out-of-brace during the bracing period were collected from the well-organized archives of OLVG. Since follow-up intervals varied widely, measurements of the in-brace group were clustered in intervals of 6 ± 3 months, starting on the date of the first in-brace radiograph until the last. In the out-of-brace group, measurements were clustered in the same intervals, but starting on the date of the last radiograph before bracing until the last out-of-brace radiograph in the bracing period. When two radiographs fell in the same time interval, their mean Cobb angle was used. Reasons for varied follow-up intervals were adjustments for patients' individual needs (first brace, growth spurt, atypical or progressive curve, poor compliance)[3]. The initial in-brace correction was only calculated for patients where the time frame between pre-brace measurement and first measurement in-brace did not exceed 6 months.

Statistical analysis

Patient characteristics comparability was assessed using independent sample t-test for continuous variables and the chi-square test for categorical variables. Curve progression was calculated by subtracting patients' Cobb angle at the first included in-brace or out-of-brace radiograph from the Cobb angle at the following six-monthly intervals. A one-sample t-test was used to test for differences between the degree of curve progression in each group at the end of the brace treatment and zero, which stands for no curve progression. An independent t-test was used to test for differences in curve progression between both groups. Analysis of curve progression measures over time was conducted with linear mixed models for repeated measures with restricted maximum likelihood estimation, with adjustment for baseline Cobb angle score and initial in-brace correction and time included as a linear term. Possible interaction effects for group and time, baseline Cobb angle score (patients' Cobb angle at the first included radiograph in-brace or out-of-brace) and time, and initial in-brace correction and time were examined. To evaluate whether the ability to detect curve progression over time with the in-brace protocol was non-inferior compared to the out-of-brace protocol, a non-inferiority analysis was performed. Since the recognized measurement error in measuring Cobb angles is

5 degrees, a non-inferiority margin of 5 degrees was used for the yearly curve progression rate[3]. This results in a non-inferiority margin of 0.4 degrees in monthly progression rate, which will be presented in the results as outcome measure. The in-brace protocol is considered non-inferior when the 95% confidence interval (CI) of the monthly progression rate does not exceed the non-inferiority margin of 0.4 degrees. SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A P-value <0.05 was considered to be statistically significant.

Results

Patient characteristics

Twenty-five patients fulfilled the inclusion criteria for the in-brace group with in-brace follow up radiographs (Table 2). The mean age at surgery was 15.0 years (SD=1.6) and twenty-two patients (88%) were female. The mean pre-brace Cobb angle was 40 degrees, and the mean preoperative Cobb angle out-of-brace was 58 degrees. The mean duration of treatment with a Boston brace was 4.1 years.

The out-of-brace group consisted of 26 patients with failed brace treatment which received out-of-brace follow up radiographs. There were no significant differences in mean age at start Boston brace treatment, age at surgery, gender ratio, pre-brace Cobb angle, number of patients with pre-brace Lenke classification curve type 1, brace initiation before menarche ratio, study follow-up duration, duration of brace treatment, and preoperative Cobb angle out-of-brace between the two groups (Table 2)[12]. But the percentage initial in-brace correction was significant larger in the out-of-brace group (37%) compared to the in-brace group (20%, P<0.01).

Table 1: Patient characteristics

Criterion	N	In-brace group (N = 25)	N	Out-of-brace group (N = 26)	P-value
Gender, female (%)	25	22 (88.0%)	26	24 (92.3%)	0.61
Age at start Boston brace treatment	25	11.0 ± 2.7	26	11.7 ± 2.0	0.26
Pre-brace Cobb angle	18	40.0 ± 7.4	26	37.7 ± 7.8	0.32
Pre-brace Lenke classification, curve type 1 (%)[10]	25	20 (80%)	26	24 (92%)	0.20
Brace initiation before menarche (%)	21	15 (71.4%)	24	19 (79.2%)	0.55
Initial in-brace correction	18	19.5% ± 16.4	21	37.3% ± 18.1	<0.01*
Study follow-up duration (years)	25	3.4± 2.0	26	3.3 ± 1.3	0.78
Duration of brace treatment (years)	25	4.1 ± 2.1	25	3.6 ± 1.6	0.37
Age at surgery	25	15.0 ± 1.6	25	15.3 ± 1.8	0.57
Preoperative Cobb angle out-of-brace†	11	57.9 ± 8.0	26	52.5 ± 9.7	0.11

Values are presented as mean ± standard deviation
Abbreviations: N, number of patients in which criterion could be determined; IS, idiopathic scoliosis

Curve progression of scoliosis

Figure 1 presents Cobb angle progression over time of the in-brace and out-of-brace group. In both groups significant curve progression was observed compared to baseline during the bracing period (P < 0.01). The mean curve progression at the end of the follow-up was 22.9 ± 15.3 degrees in the in-brace group versus 15.2 ± 7.9 degrees in the out-of-brace group (P = 0.03, see table 3). Only at the first follow up moment, curve progression was significantly higher in the in-brace group compared to the out-of-brace group with a mean difference of 6.6 degrees in Cobb angle. The mean difference of curve progression at the end of brace treatment was 7.6 degrees.

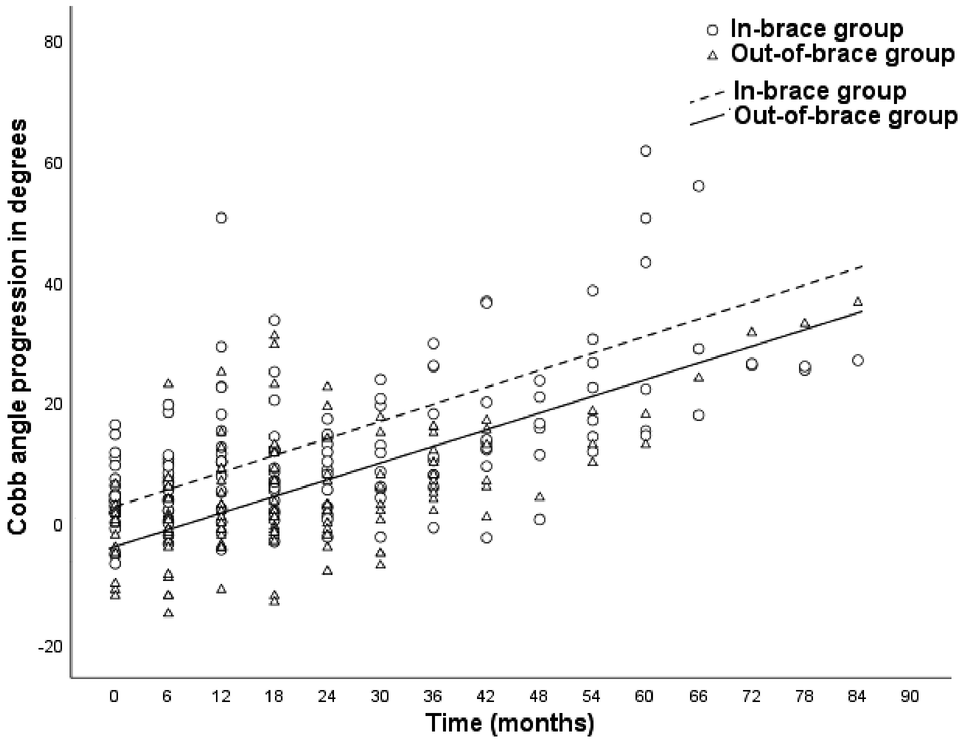

Figure 1: Cobb angle progression over time of the in-brace group and out-of-brace group
*Cobb angle measurements on follow-up radiographs were clustered in time intervals of 6 months ± 3 months. The formulas for the estimated monthly Cobb angle progression in the in-brace (2.8+0.5*x) and out-of-brace group (-3.8+0.5*x) were formed using the mixed effect model with adjustment for baseline Cobb angle score and initial in-brace correction and time included as a linear term*

No significant differences in Cobb angle curve progression across time was established between the in-brace and out-of-brace group (P = 0.80). Also no interaction effect was found for time and patients' baseline Cobb angle (P = 0.98), and for time and patients' initial in-brace correction (P = 0.32). The estimated monthly Cobb angle progression based on the mixed effect model was 0.5 degrees in both the in-brace and out-of-brace group (Table 3). The criteria for non-inferiority were met, as the 95% CI did not exceed the predefined non-inferiority margin of 0.4 Cobb angle degrees. The mean study follow-up duration was 3.4 ± 2.0 years for the in-brace group and 3.3 ±1.3 years for the out-of-brace group (P = 0.78).

Table 3: Curve progression over time

Measurement	Estimate in CA In-brace group	Estimate in CA Out-of-brace group	Mean difference	SEΔ	P-value	95% CIΔ
Mean curve progression†	22.9 (SD=15.3)	15.2 (SD=7.9)	7.62	3.40	0.03*	0.80 – 14.45
Monthly curve progression‡	0.47	0.46	0.01	0.05	0.79	-0.08 – 0.10

†Curve progression was calculated by subtracting patient's baseline CA from CA at end of brace treatment. An independent t-test was used to compare the degree of curve progression between both groups

‡The estimated monthly Cobb angle progression was based on the mixed effect model

**indicates a statistically significant difference (P<0.05)*

Measurements are expressed in Cobb angle degrees

Abbreviations: CA, Cobb Angle; SD, standard deviation; SEΔ, standard error of difference; CIΔ, confidence interval of difference

Discussion

In this study two standardized protocols for follow-up radiographs (in-brace versus out-of-brace radiographs) from two different medical clinics were compared for the ability to detect clinically relevant curve progression over time in idiopathic scoliosis patients with failure of brace treatment. Only at the first follow up visit, curve progression was significantly higher in the in-brace group compared to the out-of-brace group with a mean difference of 6.6 degrees in Cobb angle. This difference can be explained by the difference in baseline measurement, as the first radiograph in-brace was used as a reference for the in-brace group. In the out-of-brace protocol, the index radiograph just before the start of brace treatment was used as reference for future measurements. The radiograph that checks the correction and effectiveness of the brace cannot be used as a reference in the out-of-brace protocol. Since curves do not completely return to their original severity after temporary discontinuation of the brace, the out-of-brace group has a negative mean curve progression at the first follow-up visit. This explains the difference in progression at the start. After this first measurement, the rate of curve progression was not statistically significant any more between both groups. Consequently, this study shows that the protocol with in-brace radiographs was non-inferior regarding curve progression rate over time. However, switching between protocols results in a temporary inability to detect curve progression.

To our knowledge, there are no studies analyzing both in-brace and out-of-brace follow-up protocols for the ability to detect curve progression over time. The SOSORT bracing protocol recommends quality check of the brace through an in-brace radiograph (level IV of evidence), and regularly performed out-of-brace radiographs to examine the effectiveness of bracing treatment (level V of evidence)[3]. In literature, studies investigating curve progression in IS patients treated with brace therapy generally used out-of-brace radiographs at follow up moments[10, 13].

When interpreting the results of this study a few limitations should be considered. This study was designed to determine and compare the rate of curve progression for both follow up protocols. Therefore, only patients with curve progression were selected. This patient group was, however, considered as the most relevant for this study's research question. Another limitation of this study is that the reason for failure of the brace treatment could not be investigated with the current study design. Furthermore, the results of this study were not based on an experimental study design but on retrospective observations. Although this study did not focus on predictive factors for curve progression, the patient characteristics were comparable between the in-brace and out-of-brace group, except for the initial-in-brace correction. In both groups the mean initial-in-brace correction was less than 45%, which is associated with brace treatment failure. Although the in-brace correction has been described as an important predictive factor for brace failure, a minimum threshold has not been established. Previous studies have reported optimal cut-off values for initial in-brace correction varying between less than 10% to 45% predictive for brace treatment failure[14, 15]. In our study, 11.8% of the patients had an initial in-brace correction of less than 10%, whereas 84% of the patients had an initial in-brace correction of less than 45%. There was no interaction effect found for time and patients' initial in-brace correction (P=0.32). Therefore, the 18% difference in mean initial in-brace correction between both groups has probably not influenced the rate of curve progression. Other limitations are the relatively small patient groups and variation in follow-up intervals among included patients. No power analysis was performed. This was not considered as a problem for the interpretation of this study's results, since the 95% confidence interval of the difference in monthly curve progression between the in-brace and out-of-brace group was very small (-0.09 – 0.12 degrees in Cobb angle) and within the non-inferiority marge of 0.4 degrees. So far, there are no evidence based protocols and current follow-up is based on an international consensus [3]. When signs of treatment failure were detected, physicians tended to deviate from this consensus to monitor patients more closely, which could explain the variation in follow-up intervals. A final limitation of this study is that a possible lack of compliance to the brace treatment was not monitored, which is an important factor for treatment failure.

The main therapeutic goal of bracing is to halt the scoliosis curves from progression and prevent the need for surgical treatment. During brace treatment, patients are regularly seen to check proper brace fit and verify its usefulness[3]. The early detection of curve progression could be important for motivational reasons to improve brace compliance. Often, out-of-brace protocols for radiologic follow up include temporary discontinuation of the brace, as it allows visualization of progression above the curve size at the start of treatment. On the contrary, the major advantage of in-brace radiographic follow-up is that proper curve correction can be evaluated and brace corrections can be made if necessary. The theoretical drawback of in-brace follow-up radiographs is decreased detectability of curve progression due to partial correction of the curve by the brace. This study shows that the ability to detect curve progression is similar in two cohorts of patients with in-brace and out-of-brace radiologic follow up protocols. Switching between protocols during the brace treatment would not be recommended, as this results in a period in which a physician is blinded for progression since the reference radiographs vary between protocols. However, when progression is demonstrated on subsequent follow-up radiographs and the major curve Cobb angle is exceeding 40 degrees, a one-time switch from the protocol with in-brace radiographs to the protocol with out-of-brace radiographs should be considered. This is because curves exceeding 45-50 degrees are often treated surgically, and out-of-brace radiographs can provide more useful information for clinical decision making[4-7]. Despite that the protocol with in-brace radiographs was non-inferior in this study regarding curve progression rate over time, the severity of the major curve Cobb is still underestimated with an in-brace radiograph. A potential delay in surgical treatment could occur, and therefore the out-of-brace protocol is preferred for potential surgery candidates. For non-potential surgery candidates. for example patients with a major scoliosis curve below 40 degrees, a clinician might consider using the protocol with in-brace radiographs in order to evaluate the curve correction at each follow-up moment so that brace corrections can be made if necessary.

Conclusion

In conclusion, this study shows that the rate of curve progression is similar in patients with failed brace treatment when checked with in-brace and out-of-brace radiologic follow-up protocols. For potential surgery candidates with larger major curve Cobb angles, the protocol with out-of-brace radiographs or a switch from protocol with in-brace radiographs to out-of-brace radiographs is, however, preferred in daily practice, since out-of-brace radiographs can provide more useful information for clinical decision making. For patients with smaller scoliosis curve, the protocol with in-brace radiographs can be considered in order to evaluate the curve correction so that brace corrections can be made if necessary.

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CHAPTER 7

Validity and reliability of the adapted Dutch version of the Brace Questionnaire (BrQ)

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(submitted)

Abstract

Purpose: The Brace Questionnaire (BrQ) is a disease-specific health-related quality of life (HRQOL) instrument for measuring perceived health status of scoliosis patients undergoing brace treatment. It consists of 34 Likert-scale brace-related questions grouped in eight domains. The purpose of this study is to evaluate the validity and reliability of a translated and culturally adapted Dutch version of the BrQ.

Methods: The original Greek BrQ was translated into Dutch and a cross-cultural adaption and validation processes were conducted. Subsequently, 80 adolescent idiopathic scoliosis (AIS) patients undergoing active brace treatment were included from four scoliosis centers to evaluate the validity and reliability of the Dutch version of the BrQ. The questionnaire's floor and ceiling effects, internal consistency and test-retest reliability were assessed. Concurrent validity was evaluated by comparing the BrQ with the revised Scoliosis Research Society 22-item questionnaire (SRS-22r) scores.

Results: The mean total BrQ score was 75.9 (SD=11.3) and the mean domain scores varied between 3.37 (SD=0.88) and 4.22 (SD=0.66) for the domain "vitality" and "bodily pain", respectively. There were no floor and ceiling effects for the total BrQ score. The BrQ showed satisfactory internal consistency in most subdomains with a Cronbach's α ranging between 0.35 for the domain "general health perception" and 0.89 for the domain "self-esteem and aesthetics". Excellent test-retest reproducibility was observed for the total BrQ score (ICC=0.91), and the BrQ was successfully validated against the SRS-22r.

Conclusion: The translated and culturally adapted Dutch version of the BrQ is a valid and reliable HRQOL instrument for AIS patients undergoing brace treatment.

Introduction

Bracing of adolescent idiopathic scoliosis (AIS) is effective to decrease the progression risk and subsequent need for surgical treatment[1]. The success rate of bracing is mainly associated with compliance as significant positive association between hours of brace wear and rate of treatment success has been observed[1-3]. Generally, studies have reported a low compliance and many factors likely to contribute to this low compliance, including comfort, social issues, and self-image[3, 4]. A disease-specific health-related quality of life (HRQOL) measurement could provide better insights on the impact of brace wear on different health domains, in order to improve compliance and subsequently long-term treatment success[5].
The revised Scoliosis Research Society22-item questionnaire (SRS-22r) assesses the overall HRQOL of AIS patients but does not contain a specific item on the influence of brace therapy on HRQOL[6]. Therefore, the Brace Questionnaire (BrQ) was developed as a new instrument for measuring HRQOL of scoliosis patients undergoing brace treatment[7]. The BrQ consists of 34 Likert-scale brace-related items, which are grouped in eight domains (general health perception, physical functioning, emotional functioning, self-esteem and aesthetics, vitality, school activity, bodily pain, and social functioning)[7]. The original Greek BrQ has previously been translated into different languages and validated but has not yet been translated into the Dutch language[8-15]. Therefore, this study will evaluate the validity and reliability of a translated and culturally adapted Dutch version of the BrQ.

Methods

Translation and cross-cultural adaption process

This study was approved by the Medical Ethical Review Board (RR-Number: 202100536) and carried out in four scoliosis centers in the Netherlands. The translation and cross-cultural adaption process were conducted in accordance with previously described guidelines[16]. First, two independent native Greek speakers, of whom one has a medical background, have translated the original Greek BrQ into Dutch. These translations were merged into one Dutch version by both translators and a recording observer (CP) who guided the translation and adaption process. All discrepancies were solved by consensus. Subsequently, a blinded back translation from Dutch into Greek was performed by two other independent native Greek speakers of whom one has a medical background. Finally, all translations were reviewed and a prefinal Dutch version was created during an expert committee meeting. Four translators including two language professionals, two orthopaedic spine surgeons (DK and CF), and the recording observer attended the meeting. In this meeting the semantic, idiomatic, experiential and conceptual equivalences between the original Greek BrQ and prefinal Dutch version were also examined. For the pretest 32 AIS patients, between 11 and 16 years old (23% male), completed the prefinal Dutch version of the BrQ and were asked for any difficulties in interpretation of the questions and answers. Since no difficulties in interpretation were experienced and only two words `("with scoliosis") were added to Question 13 for better understanding, a second consultation of the expert committee was unnecessary. The final version of the Dutch BrQ after cross-cultural testing is shown in Supplementary data 1.

Study procedure

Patients from four scoliosis centers were prospectively included in this multicenter study from April 2022 to January 2023 according to the following inclusion criteria: They were diagnosed with AIS (i), aged between 12-18 years (ii), Dutch-speaking (iii), and undergoing active brace treatment for at least 3 months (iv). Patients with non-idiopathic scoliosis or previous spinal surgery were excluded. Eligible patients were asked for participation at the outpatient clinic or by telephone. After obtaining informed consent, included patients received a link to two questionnaires by email: (1) the final adapted Dutch version of the BrQ, and (2) the Dutch version of the SRS-22r for comparison and concurrent validity[6]. The SRS-22r questionnaire has been successfully translated and validated previously into Dutch and was used in previous BrQ validation studies in other languages as a scoliosis specific quality of life questionnaire[6, 8, 10, 12, 13, 15]. Both questionnaires were sent twice to investigate the test-retest reliability. After completing the first questionnaires, patients received a second link by email after an interval of 10-14 days. The patient could only complete the electronic questionnaire if all questions were answered.

Statistical analysis

The scoring of the questions and domains of the Dutch version of the BrQ and SRS-22r was performed according to the corresponding scoring guidelines[6, 7, 17]. Both questionnaire scores range from 1 (minimum score) to 5 (maximum score). For the BrQ items 4, 5, 6, 12, 14, 15, 16 and 17, the answer "always" received a score of 5, and "never" a score of 1. For the other 26 BrQ items, the answer "always" received a score of 1, and "never" a score of 5.

Subsequently, each item score is multiplied by 20 and the total score is divided by 34, resulting in a total minimum score of 20 and maximum score of 100. A higher score indicates better HRQOL[7]. Regarding the SRS-22r scoring system, total scores range between 5 and 25 for the domains function, pain, self-image and mental health, and between 2 and 10 for satisfaction/dissatisfaction with management[6]. The average scores vary between 1 and 5 for all domains, where a higher score indicates better HRQOL.

For both the BrQ and SRS-22r, the mean, standard deviation (SD), range, floor and ceiling effects were determined per domain. Floor and ceiling effects were assessed by calculating the frequency of lowest and highest possible domain scores. The reliability of the BrQ was assessed and compared with the SRS-22r by determining the internal consistency and reproducibility, respectively. Cronbach's α was used to evaluate internal consistency of each domain. A Cronbach's α of >0.80 represents excellent internal consistency, a Cronbach's α of 0.70-0.80 represents good internal consistency, and <0.70 represents poor internal consistency[6]. Reproducibility was evaluated by a test-retest reliability analysis for the total score and per domain of the first and second measurement, using an intraclass correlation coefficient (ICC) (one-way random). An ICC larger than 0.8 is considered to indicate excellent reliability, and a value of 0.7-0.8 indicates good reliability[6, 18].

Concurrent validity was assessed by comparing the mean scores of four BrQ domains (physical functioning, emotional functioning, self-esteem and aesthetics, and bodily pain) with four comparable domains of the SRS-22r (function, mental health, self-image, pain) using Pearson's correlation coefficient[10, 13]. A Pearson's rho of >0.70 is considered to represent excellent concurrent validity, a rho of 0.50-0.70 represents good validity, and <0.50 represents poor validity[6]. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. A P-value <0.05 was considered as statistically significant.

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Results

Patient characteristics

80 AIS patients undergoing active brace treatment gave their informed consent and were included in this multicenter validation and reliability study of the Dutch version of the BrQ (Table 1). The number of inclusions per center varied between 13 and 31. The response rate was 72% and varied per center (39% to 94%). Fifty-seven included patients (71.3%) completed both sets of questionnaires. The mean age at study inclusion was 14.3 years (SD=1.4), and 60

patients (75%) were female. A Boston brace was used in 99% of the included patients, one patient wore a Cheneau brace. The mean pre-brace major curve Cobb angle was 37.7 degrees (SD=11.6), and the self-reported mean number of hours of brace wear per day during the past month was estimated at 15.5 hours (SD=6.5).

Table 1: Patient characteristics

Criterion	N	Study population
Female gender*	80	60 (75.0%)
Postmenarchal at study inclusion*	60	44 (73.3%)
Age at brace initiation in years†	80	12.7 ± 1.7
Age at study inclusion in years†	80	14.3 ± 1.4
BMI at study inclusion†	80	18.0 ± 2.9
Risser stage[21] at study inclusion*, Risser 0	80	18 (22.5%)
I		7 (8.8%)
II		10 (12.5%)
III		15 (18.8%)
IV		29 (26.3%)
V		1 (1.3%)
Pre-brace Cobb angle†	78	37.7 ± 11.6
Initial in-brace correction in %†	70	28.8 ± 17.1
Cobb angle at study inclusion†[1]	80	35.9 ± 13.6
Lenke classification[22] before surgery*, Lenke type 1	80	50 (62.5%)
Lenke type 5		19 (23.8%)
Lenke type 2, 3, 4 or 6		11 (13.8%)
Daily hours of brace wear†[2]	80	15.5 ± 6.5

**Values are presented as number (percentage).*
†Values are presented as mean ± standard deviation.
[1]Measured on the last in-brace or out-of-brace radiograph before study inclusion.
[2]Patients were asked to estimate their average number of hours of brace wear per day during the past month of brace treatment.
Abbreviations: N, number of patients in which criterion could be determined; BMI, body mass index.

Total and domain scores

The mean total BrQ score for this Dutch study population was 75.9 (SD=11.3) and the mean domain scores of the eight different BrQ domains varied between 3.37 (SD=0.88) for the domain “vitality” and 4.22 (SD=0.66) for the domain “bodily pain” (Table 2). There were no floor and ceiling effects for the total BrQ score. Also, no floor effects were observed for the BrQ domains, but ceiling effects between 1.3% and 15% were observed for all BrQ domains. Regarding the SRS-22r, the mean total score was 3.89 (SD=0.57) and the domain scores varied between 3.48 (SD=0.83) for the domain “self-image” and 4.36 (SD=0.52) for the domain “function”. There were also no floor and ceiling effects for the total SRS-22r score. Ceiling effects between 2.5% and 16.3% were observed for all SRS-22r domains.

Table 2: Domain scores of the BrQ and SRS-22r (80 patients)

Domain (N)	Mean ± SD	Range	Floor effect (%)[1]	Ceiling effect (%)[1]
BrQ				
General health perception (2)	3.66 ± 0.79	2.00 – 5.00	0	6.3
Physical functioning (7)	3.60 ± 0.65	1.71 – 5.00	0	1.3
Emotional functioning (5)	3.63 ± 0.88	1.60 – 5.00	0	5.0
Self-esteem and aesthetics (2)	3.46 ± 0.90	1.50 – 5.00	0	10.0
Vitality (2)	3.37 ± 0.88	1.00 – 5.00	1.3	5.0
School activity (3)	3.91 ± 0.78	1.67 – 5.00	0	13.8
Bodily pain (6)	4.22 ± 0.66	2.33 – 5.00	0	15.0
Social functioning (7)	3.95 ± 0.75	1.57 – 5.00	0	6.3
Total BrQ score	75.9 ± 11.3	52.9 – 95.3	0	0
SRS-22r				
Function (5)	4.36 ± 0.52	3.00 – 5.00	0	16.3
Pain (5)	4.11 ± 0.71	1.40 – 5.00	0	8.8
Self-image (5)	3.48 ± 0.83	1.60 – 5.00	0	2.5
Mental health (5)	3.63 ± 0.84	1.00 – 5.00	1.3	2.5
Satisfaction/dissatisfaction with management (2)	3.81 ± 0.73	2.00 – 5.00	0	8.8
Total SRS-22r score	3.89 ± 0.57	2.23 – 4.77	0	0

[1]Floor and ceiling effects are the percentage of patients who scored the lowest or highest possible domain score, respectively.

Abbreviations: BrQ, Brace Questionnaire; SRS-22, revised Scoliosis Research Society 22-item questionnaire; N, number of questions per domain; SD, standard deviation.

Internal consistency and reproducibility

The Cronbach's α of the eight different BrQ domains ranged between 0.35 for the domain "general health perception" and 0.89 for the domain "self-esteem and aesthetics" (Table 3). The Cronbach's α of the five SRS-22r domains varied between 0.57 and 0.85. The test-retest reproducibility was excellent for both the BrQ (ICC=0.91, 95% CI=0.85–0.94) and SRS-22r (ICC=0.87, 95% CI=0.79–0.92). The ICC's of the BrQ domains varied between 0.62 for the domain "self-esteem and aesthetics" and 0.86 for the domain "bodily pain", and the ICC's of the SRS-22r domains varied between 0.64 and 0.85 (Table 3). The average time between the first and second measurement was 28.4 days (SD=16.6).

Table 3: Internal consistency and test-retest reproducibility of the BrQ and SRS-22r domains

Domain (N)	Internal consistency Cronbach's α	Test-retest reproducibility ICC (95% CI)
BrQ total		0.91 (0.85 – 0.94)
General health perception (2)	0.35	0.67 (0.50 – 0.79)
Physical functioning (7)	0.55	0.82 (0.71 – 0.89)
Emotional functioning (5)	0.80	0.79 (0.67 – 0.87)
Self-esteem and aesthetics (2)	0.89	0.62 (0.43 – 0.76)
Vitality (2)	0.70	0.79 (0.67 – 0.87)
School activity (3)	0.59	0.72 (0.57 – 0.82)
Bodily pain (6)	0.78	0.86 (0.78 – 0.92)
Social functioning (7)	0.78	0.80 (0.69 – 0.88)
SRS-22r total		0.87 (0.79 – 0.92)
Function (5)	0.64	0.74 (0.60 – 0.84)
Pain (5)	0.80	0.77 (0.64 – 0.86)
Self-image (5)	0.79	0.85 (0.75 – 0.91)
Mental health (5)	0.85	0.77 (0.64 – 0.86)
Satisfaction/dissatisfaction with management (2)	0.57	0.64 (0.45 – 0.77)

Abbreviations: BrQ, Brace Questionnaire; SRS-22, revised Scoliosis Research Society 22-item questionnaire; N, number of questions per domain; ICC, interclass correlation coefficient; CI, confidence interval

Concurrent validity

A statistically significant concurrent validity was established for the total BrQ and total SRS-22r scores (Table 4). Also, the BrQ domains "physical functioning", "emotional functioning", "self-esteem and aesthetics", and "bodily pain" correlated significantly with the comparable domains of the SRS-22r (function, mental health, self-image, pain). The Pearson's rho correlation coefficient varied between 0.41 for the BrQ domain "physical functioning" and 0.64 for the BrQ domain "bodily pain".

Table 4: Concurrent validity of the BrQ domains in relation to comparable SRS-22r domains

Domain BrQ	Domain SRS-22r	Pearson's rho	P-value
Physical functioning	Function	0.41	<0.001*
Emotional functioning	Mental health	0.63	<0.001*
Self-esteem and aesthetics	Self-image	0.51	<0.001*
Bodily pain	Pain	0.64	<0.001*
Total score BrQ	**Total score SRS-22r**	0.79	<0.001*

**Indicates a statistically significant difference (P<0.05)*
Abbreviations: BrQ, Brace Questionnaire; SRS-22, revised Scoliosis Research Society 22-item questionnaire

Discussion

The aim of this study was to translate and culturally adapt the original Greek BrQ into the Dutch language and to evaluate the validity and reliability of this Dutch version. The BrQ was successfully translated and adapted, and the Dutch version of the BrQ showed no floor and ceiling effects for the total BrQ score, excellent test-retest reproducibility, and satisfactory internal consistency in most subdomains. Also, a satisfactory concurrent validity was found for the BrQ domains "physical functioning", "emotional functioning", "self-esteem and aesthetics", and "bodily pain". The mean total BrQ score for this Dutch study population was 75.9 (SD=11.3), which is comparable to population groups in other countries[8, 11, 14].

Generally, a minimum Cronbach's α of 0.70 is recommended for satisfactory internal consistency of a scale[7]. The Cronbach's α's of the eight subdomains in the present study varied (0.35 – 0.89) and were slightly lower than in most other BrQ validation studies[7, 11-13]. The Cronbach's α is impacted by the number of items. Therefore, a lower α coefficient may be expected with only three or less items, what could explain the relatively low Cronbach's α of 0.35 for the domain "general health perception", which consists of two questions, and the Cronbach's α of 0.59 for the domain "school activity", which consists of three questions. The relatively low Cronbach's α of 0.55 for the domain "physical functioning" was more remarkably as the domain consists of seven questions. Using the "Cronbach's α if item deleted" procedure, the exclusion of item 5 ("you managed to wear the brace without any help") improved the Cronbach α to 0.67. Since brace type and age could influence the score for this item, these factors could be possible explanations for the improvement of internal consistency. The ceiling effect percentages per domain in the present study were slightly higher compared to most other BrQ validating studies in literature, but did not exceeds 15% [7, 9, 11, 12, 14]. For the overall BrQ score, no floor or ceiling effects were observed. Although the average time between the first and second measurement was relatively long (28.4 days, SD=16.6), the test-retest reproducibility was excellent for the overall BrQ score (ICC=0.91), which was also comparable with literature[10, 12-14].

Clinical implications

As the generally low compliance rates during brace treatment of AIS remains a challenge for healthcare professionals, further knowledge about the impact of brace wear and the effect of new brace modifications or brace-related interventions on different HRQOL domains could lead to new insights for better brace compliance. The SRS-22r assesses the overall HRQOL of AIS patients, but does not contain a specific item on the influence of brace therapy on HRQOL. The results of this study prove that the BrQ can be used reliable in the Dutch population group. Overall, the BrQ and SRS-22r questionnaires showed comparable floor and ceiling effects, internal consistency and reproducibility between the two questionnaires. However, the BrQ contains specific items on the influence of the brace treatment on HRQOL. This might help to provide a better insight on the impact of bracing during clinical monitoring of patients. It is important to identify the patients undergoing active brace treatment who are scoring below the norm, in order to provide additional brace adjustments, extra monitoring, and proper support of the physician, the parents, and/or a psychologist in the form of individual sessions or group sessions[20]. In addition, future studies using the BrQ could help identify patient characteristics influencing under average scoring HRQOL domains. This could provide more specific information on which patient group clinicians should pay extra attention.

Limitations

A few limitations should be considered when interpreting this study's results. The patient sample size with 80 patients was considered large enough for the validity and reliability assessment, but not large enough to test the discriminative ability of the BrQ. Therefore, this was not tested in this study. It is, however, highly questionable whether a larger patient sample alone would be sufficient to provide a reliable overview of the discriminative ability of the BrQ. In order to explore the discriminative ability, it might be better to use the BrQ at biannual time-intervals during the whole bracing period in multi-center, long-term longitudinal follow-up studies, since the impact of brace wear for the individual AIS patient can change over time. Another limitation of this study was that 99% of the patients wore a Boston brace. Different types of braces could have a different effect on HRQOL scores.

Conclusion

The translated and culturally adapted Dutch version of the BrQ proved to be a valid and reliable HRQOL measuring instrument for AIS patients undergoing brace treatment. Therefore, this instrument is considered useful as a clinical evaluation tool for both clinical and research purposes for the Dutch AIS group during brace treatment.

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Supplementary data

BRACE VRAGENLIJST

De volgende vragenlijst is een vertaalde vragenlijst vanuit het Grieks en bevat vragen over wat je over je gezondheid denkt en voelt. Het is geen test en er zijn geen goede of foute antwoorden

- ***Lees elke vraag aandachtig***
- ***Kies het antwoord waarvan jij denkt dat het beste bij je past. Zet een kruisje in het vakje ernaast***

Voorbeeld	Nooit	Zelden	Soms	Vaak	Continu
Gedurende de afgelopen week had ik zin in lezen	☐	☐	☐	x	☐

Zou je ons een paar dingen over jezelf willen vertellen?

Je bent: ☐een meisje ☐een jongen Leeftijd: ....jaar

Datum...

7

Gedurende de afgelopen 3 maanden...	Nooit	Zelden	Soms	Vaak	Continu
1. Zorgde de brace ervoor dat je je ziek voelde	☐	☐	☐	☐	☐
2. Was je bang dat je scoliose erger zou worden	☐	☐	☐	☐	☐

Gedurende de afgelopen 3 maanden...	Nooit	Zelden	Soms	Vaak	Continu
3. Werd je moe van het lopen vanwege de brace	☐	☐	☐	☐	☐
4. Kon je rennen met de brace	☐	☐	☐	☐	☐
5. Trok je de brace zonder hulp aan	☐	☐	☐	☐	☐
6. Trok je de brace zonder hulp uit	☐	☐	☐	☐	☐
7. Kon je niet goed eten vanwege de brace	☐	☐	☐	☐	☐
8. Kon je niet goed slapen vanwege de brace	☐	☐	☐	☐	☐
9. Kon je niet goed ademen vanwege de brace	☐	☐	☐	☐	☐

Gedurende de afgelopen 3 maanden...	Nooit	Zelden	Soms	Vaak	Continu
10. Maakte de brace je nerveus	☐	☐	☐	☐	☐
11. Voelde je je verdrietig vanwege de brace	☐	☐	☐	☐	☐
12. Voelde je je gelukkig	☐	☐	☐	☐	☐
13. Geloofde je dat je leven met scoliose beter zou zijn geweest als je geen brace zou hebben gedragen	☐	☐	☐	☐	☐
14. Geloofde je dat de brace-behandeling nuttig was	☐	☐	☐	☐	☐

Gedurende de afgelopen maand...	Nooit	Zelden	Soms	Vaak	Continu
15. Was je trots op jezelf	☐	☐	☐	☐	☐
16. Was je tevreden over jezelf	☐	☐	☐	☐	☐

Gedurende de afgelopen maand...	Nooit	Zelden	Soms	Vaak	Continu
17. Voelde je je sterk en vol energie	☐	☐	☐	☐	☐
18. Voelde je je moe en uitgeput vanwege de brace	☐	☐	☐	☐	☐

Gedurende de afgelopen maand...	Nooit	Zelden	Soms	Vaak	Continu
19. Had je moeite in de les vanwege de brace	☐	☐	☐	☐	☐
20. Miste je weleens school vanwege de brace	☐	☐	☐	☐	☐
21. Lette je niet op in de klas	☐	☐	☐	☐	☐

Gedurende de afgelopen maand...	Nooit	Zelden	Soms	Vaak	Continu
22. Nam je medicijnen omdat je pijn had	☐	☐	☐	☐	☐
23. Had je ’s nachts pijn	☐	☐	☐	☐	☐
24. Had je pijn bij het lopen	☐	☐	☐	☐	☐
25. Had je pijn bij het zitten	☐	☐	☐	☐	☐
26. Had je pijn bij het traplopen	☐	☐	☐	☐	☐

7

27. Kreeg je door de brace tintelingen in je handen of voeten	☐	☐	☐	☐	☐

Gedurende de afgelopen maand...	**Nooit**	**Zelden**	**Soms**	**Vaak**	**Continu**
28. Kon je je vrienden niet zien vanwege de brace	☐	☐	☐	☐	☐
29. Hadden je vrienden medelijden met je vanwege je rug	☐	☐	☐	☐	☐
30. Voelde je je anders dan je vrienden omdat je een brace draagt	☐	☐	☐	☐	☐
31. Had je problemen met je familie vanwege de brace	☐	☐	☐	☐	☐
32. Geloofde je dat je band met je familie of vrienden beter zou zijn geweest als je geen brace gedragen zou hebben	☐	☐	☐	☐	☐
33. Bleef je thuis omdat je je voor de brace schaamde	☐	☐	☐	☐	☐
34. Droeg je speciale kleding vanwege de brace	☐	☐	☐	☐	☐

CHAPTER 8

General discussion and future perspectives

Introduction and summary of the major findings of this thesis

An important clinical study about the non-operative management of adolescent idiopathic scoliosis (AIS) was a randomized and preference cohort trial, published in 2013, which has shown us that brace therapy can significantly decrease the progression risk and subsequent risk for surgical treatment[1]. This study was stopped early owing to the efficacy of bracing and has contributed to the change of view of many doubting physicians who previously saw brace therapy as ineffective. Building upon this evidence, this thesis aimed to expand the knowledge about factors associated with brace treatment success in AIS as bracing is not successful in every patient. Strong evidence has been reported for the association between lack of initial in-brace correction and brace treatment failure, which is the reason that **Chapter 4 and 5** focused on influencing factors on this in-brace correction[2]. Increased curve flexibility and thoracolumbar or lumbar curve pattern were found to be favourable predictive factors, and a double major curve pattern was found to be an unfavourable predictive factor for initial in-brace correction (**Chapter 4**). The degree of torso asymmetry and segmental peak positive and negative torso displacements in brace can be analyzed with the use of patients' 3D surface and brace models, but unfortunately these parameters are not clearly associated with initial in-brace correction (**Chapter 5**). Besides initial in-brace correction, also compliance plays an essential role in the success of brace therapy[1-3]. Knowledge about the best way to monitor progression, and about the impact of brace wear and the effect of brace-related interventions on health-related quality of life (HRQOL) of scoliosis patients undergoing brace treatment could be important for motivational reasons and new insights for better brace compliance, respectively. **Chapter 6** shows that a follow-up protocol for AIS patients with in-brace radiographs is non-inferior regarding curve progression rate over time compared to a follow-up protocol with out-of-brace radiographs. In **Chapter 7** a culturally adapted Dutch version of the Brace Questionnaire (BrQ) is presented, which is found valid for clinical and research purposes. This thesis also aimed to explore the possibilities of using a biplanar low-dose X-ray device (EOS®imaging, Paris, France) as a tool for spinal length and pedicle size measurements. Knowledge about spinal length and subsequently growth of each individual AIS patient helps with accurate timing of both conservative and surgical treatment, and preoperative knowledge about pedicle sizes could contribute to the placement of an adequate amount of well-sized pedicle screws. **Chapter 2 and 3** shows that there is a good validity and reliability for both spinal length and pedicle size measurements on EOS radiographs. This chapter discusses the interpretations and implications of these major findings of this thesis, limitations of the studies, and future perspectives.

The value of EOS radiographs for spinal length and pedicle size measurements

The clinical applications of the EOS®imaging system in orthopeadics are expanding rapidly owing to several advantages. The system can, for example, provide standing low-dose radiographs of the whole spine at once, which reduces the amount of radiation substantially in comparison with conventional radiographs[4, 5]. Furthermore, it uses biplanar perpendicular radiographs with the result that images have no divergence in the vertical plane allowing more accurate two-dimensional (2D) and 3D measurements. Previous studies have shown that EOS has value for clinical practice and can be used for reliable measurements of spinal curvature and sagittal balance, but also for non-spine related measurements like pelvic tilt and acetabular cup orientation, femoral offset, and lower limb measurements[4-9]. **Chapter 2 and 3** shows that EOS can also be used for reliable spinal length and pedicle size measurements. Within the management of AIS, this may help with accurate timing of both conservative and surgical treatment, and providing a preoperative indication of needed pedicle screw diameters.

Spinal length measurements

In literature, spinal length measurements are often performed on coronal radiographs, which have the disadvantage of X-ray beam divergence and not including deviations in the sagittal plane[10-13]. Length assessments of complex 3D deformities such as a scoliosis should therefore not be performed with 2D measure methods. As the EOS 3D spinal length measurements resulted in the best representation of the true spinal length, the 3D length measure method should be preferred above spinal length measurements on individual coronal or sagittal images (**Chapter 2**). The EOS®imaging system should particularly be considered in scoliosis clinics where growth-friendly implants are used. Reliable 3D spinal length measurements and subsequently knowledge about the growth of each treated patient is essential here, since the patient's ability to grow with these implants is limited. But monitoring of the spinal growth could also be useful in the treatment of the other patients with idiopathic scoliosis. Not only for determining the duration of brace treatment and timing the potential surgery, as surgery should be postponed until the peak growth velocity of the spine has passed to prevent complications like the crankshaft phenomenon, but also for further research purposes[14]. There exists a well-known relationship between the patient's growth and development of the spinal deformity, and high spinal growth velocity during the early pubertal growth spurt is a predisposing factor for a rapid increase of the deformity[13, 15]. Monitoring of the patients' individual spinal growth spurt and its velocity by using reliable 3D spinal length measurements could therefore contribute in predicting curve progression. It would be interesting to investigate the potential predictive value of spinal growth velocity, amongst other maturity indicators that reflect growth or remaining growth potential, for the prediction of the timing of the peak growth velocity of total body height and subsequently the curve progression in the individual AIS patient[15]. A study protocol for a prospective, longitudinal cohort study to answer this research question has already been developed, with sitting height velocity, leg length velocity, shoe size velocity, foot length velocity, skeletal age, Risser sign, triradiate cartilage, menarche, Tanner stage, and EMG ratios of the paraspinal muscles as the other maturity indicators[15]. The EOS 3D spinal length measurement method would be of value to this study protocol as it represents the true spinal length better than 2D measurements on the coronal image that originally was proposed in the protocol. Aside from a cohort study with limited amount of patients and study duration, the use of a multi-center prospective longitudinal database would be even more valuable. Such large database should preferably also include other countries to discover population group differences. Ultimately, the development of an artificial intelligence algorithm based on patient-specific factors and radiological parameters calculating the individual risk of curve progression would be 'the icing on the cake'[16]. Because knowing if and when a curve will progress would prevent unnecessary brace treatments and reduce the bracing period and the number needed to treat to prevent one case of curve progression requiring surgery.

A limitation of the EOS 3D spinal length measure method is that despite good intra and interobserver reliability was observed, manual placement of measurement points may possibly be suboptimal because the visualization of vertebral endplates is not always good in the upper thoracic region due to overprojection of the shoulders. Secondly, this method is not standardized and therefore labor-intensive. When considering implementing for regular follow-up moments in standard practices and for large multi-center prospective longitudinal databases, it not realistic to expect that for every AIS patient the total spine length can be assessed and monitored easily. Ideally, this spinal length measurement would be captured in a 3D machine learning system in order to be less time-consuming. But as long as there is no automatic or easier way to achieve reliable 3D spinal lengths, this spinal length measure method would probably be used for research purposes only.

<u>Pedicle size measurements</u>

Prior to scoliosis surgery, preoperative knowledge about the pedicle size helps to maximize screw containment and minimize the risk of pedicle breach. Pedicle sizes should ideally be measured on preoperative computed tomography (CT) for the most reliable measurements. This is, however, not done routinely due to the exposure of this young population to high levels of radiation. Preoperative EOS images were suggested in **Chapter 3** as potential alternative for pedicle size measurements, as these images are generated with much lower levels of radiation and have no divergence in the vertical plane. The results have shown that visible pedicle sizes can reliable be measured on coronal EOS radiographs. In daily practice, surgeons using free-hand pedicle screw insertion methods can therefore preoperatively measure intra- and extracortical pedicle widths for an indication of the needed pedicle screw diameters for those individual pedicles. When using intra-operative 3D imaging and a pedicle screw navigation system, preoperative knowledge of pedicle sizes could reduce the intra-operative dose, as for determining the optimal screw trajectory less resolution and therefore less radiation is needed. It would be interesting to investigate whether pedicle size dimensions measured on EOS radiographs combined with a simpler intra-operative navigation system could result in a significant reduction in radiation dose without compromising accurate placement of well-sized pedicle screws. However, there is one major limitation of using the coronal EOS radiograph for pedicle size measurements in idiopathic scoliosis. Owing to vertebral rotation, pedicles on the concave side with a Nash-Moe grade score of 2-3 cannot be measured[17]. So not every pedicle can be provided with an indication of the needed pedicle screw diameter, as axial rotation can almost always be recognized in the spinal deformity of surgery candidates, especially near the apex. The pedicle size of the convex pedicle of the rotated vertebra is, unfortunately, not representative for the contralateral concave pedicle due to the asymmetry in idiopathic scoliosis[18, 19]. Furthermore, there is a systematic, small underestimation of the pedicle width measurements on EOS images for these convex pedicles with a Nash-Moe grade score of 2-3. But although surgeons should be aware of the small underestimations, these are likely clinically irrelevant, as pedicle screws generally differ 1mm in diameter sizes, while the mean differences of intra- and extracortical pedicle width measurements of Nash Moe 2-3 pedicles between EOS radiographs and intra-operative 3D images were only -0.47mm and -0.51mm, respectively.

Future studies should focus on measure instruments that can reliable measure pedicle sizes of all pedicles with less radiation than a CT-scan. Magnetic resonance imaging (MRI) has been proposed as alternative, but it was found inferior to CT for scoliosis patients, because it has poor accuracy to properly detect pedicle abnormalities[20]. The more severe the pedicle abnormality, the less diagnostic value the MRI had[20]. Particularly in spinal deformity surgery, preoperative knowledge about pedicle sizes is warranted due to the different morphometric characteristics of the pedicle dimensions[18]. Under- or oversizing of pedicle screws increases the risk of pedicle fracture and screw loosening[21]. Furthermore, in scoliotic spines, up to one third of the mid-thoracic pedicles are not appropriate for a safe intrapedicle screw placement[22]. Although a commonly accepted criteria for pedicle screw diameter selection has not been proposed in literature yet, the systematic review of studies with recommendations reported a screw diameter ranging from 80% to a maximum value of 125% of the pedicle width[21]. This is a wide range, in which higher values for maximum screw diameter / pedicle width ratio were described for pediatric populations, owing to the relative plasticity of the pedicle cortex in the pediatric spine. Since insertional torque is useful to predict screw fixation strength, future studies investigating screw diameter / pedicle width ratio in the scoliotic spine, should also include the peak insertion torque as determining factor[23].

The black box of brace manufacturing technology

In **Chapter 4**, moderate evidence is found that braces designed with computer-aided design (CAD) and manufacturing systems with or without finite element models simulation do not significantly improve initial in-brace correction, compared to braces fabricated using the conventional plaster-cast method. So far, our knowledge on working mechanisms of braces is limited and most braces are still hand-crafted by the orthotist. The introduction of new brace designing and manufacturing technologies in clinical practise allows further research in this field to obtain a better insight in the correction mechanisms of the brace. The results of the pilot study, presented in **Chapter 5**, shows that the degree of torso asymmetry and segmental peak positive and negative torso displacements in brace can be analyzed with the use of patients' 3D surface and brace models, but that unfortunately these parameters are not clearly associated with initial in-brace correction of AIS patients with Lenke 1 or 5 curves. Although the patient sample and mean initial in-brace correction compared to literature were relatively small, it is very likely that these two measurable factors in the brace model alone are not helpful in predicting the radiographic initial in-brace correction. A possible explanation for the weak and negligible correlations is that peak positive displacement does not correlate with amount of applied pressure. A comparable amount of displacement directly applied on bones, for instance, would result in a larger pressure and torso displacement compared to the same displacement on fat tissue.

In literature, there is insufficient evidence for other potential brace related factors influencing the radiographic initial in-brace correction, such as the magnitude of the corrective force over brace pads (**Chapter 4**). Since there is no evidence based consensus on the best possible manner to achieve curve correction with bracing, the experience and even intuition of the orthotist play an essential role, representing more the art than the science of medicine[24]. Future studies should try to enlighten the black box of brace manufacturing technology as the exact mechanisms to achieve curve correction remains obscure. Starting with finding brace related parameters influencing the initial in-brace correction, would be a good strategy in order to obtain knowledge where new brace design and manufacturing methods should be focusing on. It is, for example, not excluded that when segmental peak torso displacements in-brace are combined with other brace related factors like the pad location and pad pressure or patient factors like curve magnitude or curve flexibility, they could be of added value in predicting initial in-brace correction and/or improving brace comfort. Future studies on CAD brace related factors that influences initial in-brace correction should include quantifiable parameters obtained from 3D scans and models in combination with in-brace pad pressure parameters obtained with electronic pressure sensors[25, 26]. In addition, the use of 3D ultrasound system could help with the determination of the optimum pressure level and location to assist the brace design[27].

In-brace or out-of-brace protocol for radiographic follow-up of patients with scoliosis?
In clinical practice, regular follow-up radiographs are usually made at 6 month intervals to detect curve progression during the brace treatment. Early detection of curve progression is important for motivational reasons as the most important positive factors influencing brace compliance are the patient's desire to avoid surgery and to prevent curve progression[28]. According to the SOSORT bracing protocol, these follow-up radiographs should be taken out-of-brace to examine the effectiveness of treatment (level V of evidence)[29]. It allows visualization of progression above the pre-brace curve magnitude. However, **Chapter 6** shows that a similar curve progression rate over time can be expected with both in-brace and out-of-brace protocols for radiographic follow-up in patients with idiopathic scoliosis. This is interesting, because it has generally been assumed that there is decreased detectability of curve progression owing to the partial curve correction by the brace. The major advantage of in-brace radiographic follow-up is that proper curve correction can be evaluated and brace corrections can be made if necessary. The total spine length of the patient is growing during the treatment, so periodically brace adjustments are necessary, and therefore also in-brace evaluations. When protocollary adjusting and optimizing the brace position by the orthotist before the radiograph is taken, this would probably result in better in-brace corrections. To investigate the 'at home' correction, the radiographs of the in brace group were made before interventions or adjustments

by the orthotist or physician. Therefore, clinicians should be careful with the interpretation of the in brace correction values, since adjustments were made after the radiograph. Ideally, the in-brace radiograph should be repeated after the brace adjustments by the orthopaedic surgeon and orthotist to evaluate its effectiveness. It has strongly proven that lack of initial in-brace correction is associated with brace treatment failure. But the influence of periodic checking of the in-brace correction during the bracing period on long term brace success has not yet been clarified[2]. For this latter research question, it would be rather useful to make an in-brace radiograph after the brace adjustments in order to evaluate the intervention. It might be interesting to know if not only the initial in-brace correction, but also the following periodically in-brace corrections contributes to better brace treatment success. As discussed in the previous paragraph, this also helps to better understand the correction mechanisms of the brace. Although monitoring of the curve remains essential during brace treatment, future follow-up methods should exclude radiographs in order to reduce the amount of radiation to this young population group. The use of low-dose radiographs of the whole spine at once (EOS) reduces the amount of radiation substantially in comparison with conventional radiographs and could therefore be an intermediate step before new radiation free imaging techniques have been developed and validated for the evaluation of curve magnitude and in-brace correction.

<u>So, which protocol should we use for the time being?</u>

It is hard to identify one best follow-up strategy, as both in-brace and out-of-brace protocols has its advantages and disadvantages. The protocol with in-brace radiographs was also non-inferior regarding curve progression rate over time. First, switching between protocols results in a temporary inability to detect curve progression, so this would not be recommended. An one-time switch from the protocol with in-brace radiographs to the protocol with out-of-brace radiographs by exception could be considered, when progression is demonstrated on subsequent follow-up radiographs and the major curve Cobb angle is exceeding 40 degrees. This is because curves exceeding 45-50 degrees are usually treated surgically, and out-of-brace radiographs can provide more useful information for clinical decision making in these severe curves[30]. Despite the similar curve progression rate over time between the two protocols, the severity of the major curve Cobb angle is still underestimated on an in-brace radiograph.

A potential delay in surgical treatment could occur, making the out-of-brace protocol preferable for potential future surgery candidates. For non-potential surgery candidates, for example AIS patients with a major curve below 40 degrees, a clinician might consider using the protocol with in-brace radiographs in order to evaluate the curve correction at each follow-up moment so that the brace can be adjusted if necessary. Since only surgical treated patients with failed brace treatment were included in the presented study, these recommendations should be interpreted with some caution for the non-surgical treated patients. However, the included patients with proven curve progression was considered as the most relevant group for the study's research question. Furthermore, a possible lack of compliance to the brace treatment was not monitored and this is an important factor for treatment failure[1-3]. It is not known whether insufficient in-brace corrections, compliance or both were the reason for brace treatment failure in patients in **Chapter 6**. However, **Chapter 4** shows insufficient evidence for compliance as influencing factor for initial in-brace correction. This was based on one study, in which brace wearing hours were recorded on a log sheet and by an orthosis monitoring system, that reported no significant difference on in-brace correction (<40% and ≥40% correction) after 4-6 months between three groups of different hours of brace wear (0–8 hours, 9–16 hours, and 17–23 hours)[31].

Why should we use the Brace Questionnaire?

As the generally low compliance rates remains a challenge for healthcare professionals, further knowledge about the impact of brace wear and the effect of new brace modifications or brace-related interventions on different HRQOL domains could lead to new insights for better brace compliance. The revised Scoliosis Research Society 22-item questionnaire (SRS-22r) assesses the overall HRQOL of AIS patients, but does not contain a specific item on the influence of brace therapy on HRQOL[32]. For this reason, the BrQ was translated into the Dutch language, as presented in **Chapter 7.** The translated and culturally adapted Dutch version proved to be valid and reliable. The overall BrQ score, its floor and ceiling effects, internal consistency and reproducibility were comparable to previous BrQ validating studies [26, 33-38]. This suggests that the BrQ can be reliable used in the Dutch population group for AIS patients undergoing brace treatment.

A recently published systematic review, including 60 articles of which 12 used the BrQ as HRQOL instrument, discovered that self-image, mental health, and vitality are the three most frequently reported domains in scoliosis patients undergoing brace treatment[39]. But the authors mentioned in their limitation section that the influence of factors such as curve magnitude on these three domains have not been clarified yet[39]. Future studies should therefore identify patient characteristics influencing these domains in order to provide more specific information on which patient group we should pay extra attention. A long-term longitudinal follow-up study with biannual time-intervals during the whole bracing period would be preferred, since the impact of brace wear for the individual AIS patient can change over time. In addition, the BrQ could help with monitoring the effect of new brace modifications or brace-related interventions on different HRQOL domains in future brace studies. Therefore, it is warranted that the HRQOL questionnaire also has specific items on the influence of the brace treatment.

Besides for research purposes, the BrQ could be used for clinical applications as well. In daily practice, it is important to identify the patients undergoing active brace treatment who are scoring below the norm, so that additional brace adjustments, extra monitoring, and proper support of the physician, the parents, and/or a psychologist in the form of individual sessions or group sessions, can be provided[40].

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CHAPTER 9

Summary / Nederlandse samenvatting

Summary

Idiopathic scoliosis is a common but complex three-dimensional (3D) deformity of the spine, characterized by a lateral curvature of at least 10 degrees and axial rotation. Most patients with idiopathic scoliosis typically present after 10 years of age during the adolescent growth spurt and are therefore classified as adolescent idiopathic scoliosis (AIS). When untreated, idiopathic scoliosis has a risk of progression and may lead to severe trunk deformities with both restrictive and obstructive lung disease, cosmetic issues, pain, progressive functional limitations, and decreased health-related quality of life (HRQOL). For this reason, severe curves with a Cobb angle exceeding 45-50 degrees are usually treated surgically. To prevent surgical treatment, patients with smaller curves are treated with a brace during their adolescent growth spurt with the aim of maintaining the curve below 45 degrees. Brace treatment is, however, not successful in every patient and there is room for further improvements.

The general aim of this thesis was to explore the possibilities of using a biplanar low-dose X-ray device as a tool for spine related measurements, and to expand the knowledge about factors associated with brace treatment success in AIS.

Part 1. Imaging

The first part of this thesis focuses on the validation of spine length and pedicle size measurements on radiographs generated by a biplanar low-dose X-ray device (EOS®imaging, Paris, France). These EOS radiographs use substantially less radiation in comparison with computed tomography (CT) and conventional radiographs, have no divergence in the vertical plane, and allow 3D measurements using the EOS imaging software. In **Chapter 2** the validity and reliability of EOS two-dimensional (2D) and 3D spinal length measurements in patients with AIS were investigated, since knowledge about the spine length and subsequently growth of each individual AIS patient helps with accurate timing of both non-operative and operative treatment. Prior to routine EOS radiograph, a radiographic calibrated metal beads chain (MBC) was taped to the skin on the spinous processes of 50 included AIS patients to calibrate the images. By using the EOS software, both 2D and 3D spinal lengths could be measured, and they were compared with the MBC length measurements. The results showed a good validity and reliability for total, thoracic, lumbar and segmental spinal length measurements on EOS radiographs. In contrast to the 3D measurements, the 2D lengths on the individual coronal and lateral views structurally underestimated the spinal length. This is, however, not surprising since deviations in the other plane are not taken into account during the 2D measurements of the complex 3D deformity of the spine. Therefore, the 3D measurement method is preferred

above the 2D length measurements. When the EOS 3D measure method is not possible, 2D spinal length measurements on the lateral view could be preferred above measurements on the coronal view when the major curve Cobb angle is below 40 degrees.

In **Chapter 3** the application of the EOS imaging system for spine related measurements was further investigated. In this study the intra- and extracortical pedicle height and width measurements on preoperative, coronal EOS radiographs were compared with reconstructed intra-operative 3D-images of the isthmus of 203 included pedicles from patients who underwent surgery. Good validity and excellent relative intra- and interobserver reliability for the pedicle size measurements on the EOS radiographs were found. This means that surgeons using free-hand pedicle screw insertion methods can preoperatively reliably measure intra- and extracortical pedicle widths on EOS radiographs for an indication of the needed pedicle screw diameters for those individual pedicles. Well-sized pedicle screws contribute to maximize screw containment and minimize the risk of pedicle breach. Surgeons should, however, be aware of small, likely clinically irrelevant, systematic underestimation of the pedicle width measurements on EOS radiographs when measuring visible pedicles from rotated vertebrae (mean difference of EOS and 3D intracortical pedicle width measurements was -0.47 mm for pedicles with Nash Moe score 2-3).

Part 2. Brace treatment

The second part of this thesis focuses on bracing as non-operative management of AIS. Brace treatment during a number of years of the adolescent growth spurt can significantly decrease the progression risk and subsequent risk for surgical correction. However, bracing is not successful in every patient. There is strong evidence that a lack of initial in-brace correction is associated with brace treatment failure. Building on this evidence, Chapter 4 is a systematic review with a best-evidence synthesis investigating predictive factors for initial in-brace correction in idiopathic scoliosis patients. Thirty-four different reported factors were collected from 28 included studies of which 9 studies (32%) were classified as high quality studies. Strong evidence was found for increased curve flexibility, and moderate evidence for thoracolumbar or lumbar curve pattern as favourable predictive factors for initial in-brace correction. There was also moderate evidence for double major curve pattern as unfavourable predictive factor. Braces designed with computer-aided design and manufacturing systems (CAD/CAM) with or without finite element models (FEM) simulation did not significantly improve initial in-brace correction, compared to braces fabricated using the conventional plaster-cast method.

Unlike curve type and flexibility, brace designing and manufacturing technologies are factors that theoretically can be further improved by the orthotists. CAD technologies can, for example, be used to quantify the trunk in 3D and brace characteristics. In **Chapter 5** a pilot study of 25 AIS patients is presented in which the degree of torso asymmetry and segmental peak positive and negative torso displacements have been analyzed with the use of patients' 3D surface scans and brace models for potential correlations with initial in-brace correction. This pilot study showed that for Lenke type 1 and 5 curves both the degree of torso asymmetry and segmental peak torso displacements in the patients' brace model alone are not clearly associated with initial in-brace correction. However, strong conclusions cannot be reached as this was only a pilot study, and more research is warranted assessing parameters which could contribute to prediction and further improvement of initial in-brace correction.

Besides initial in-brace correction, also compliance plays an essential role in the success of a brace treatment. To improve brace compliance, early detection of curve progression during brace treatment could be important for motivational reasons. Patient's desire to prevent curve progression and to avoid surgery has been reported as the most important positive factor influencing brace compliance. In **Chapter 6** a retrospective study is presented comparing two standardized protocols for radiological follow-up (in-brace versus out-of-brace radiographs) from two scoliosis care centers on the rate of curve progression over time in 51 surgical treated idiopathic scoliosis patients after failed brace treatment. The mean follow-up period was 3.4 years, and the rate of curve progression was found similar when checked with in-brace and out-of-brace radiologic follow-up protocols with an estimated monthly Cobb angle progression of 0.5 degrees in both groups. In daily practice, the protocol with in-brace radiographs can therefore be considered for patients with relatively small curves in order to assess the in-brace curve correction so that brace corrections can be made if necessary. But for larger scoliosis curves close to the surgical threshold, the protocol with out-of-brace radiographs or a switch from protocol with in-brace to out-of-brace radiographs is preferred, since out-of-brace radiographs can provide more useful information for clinical decision making.

Another approach to get new insights for better brace compliance is to obtain first further knowledge about the impact of brace wear and the effect of new brace modifications or brace-related interventions on different HRQOL domains. This cannot be done in the Netherlands without a disease-specific HRQOL measurement for the Dutch scoliosis patients undergoing brace treatment. Therefore, in **Chapter 7** the validity and reliability of a translated and culturally adapted Dutch version of the Brace Questionnaire (BrQ) were investigated. The Dutch version of the BrQ showed excellent internal consistency and excellent test-retest reproducibility, and there were no floor and ceiling effects for the total BrQ score. Subsequently, the BrQ domains "physical functioning", "emotional functioning", "self-esteem and aesthetics", and "bodily pain" were successfully validated against the SRS-22r. Therefore, the Dutch version of the BrQ is considered useful as a clinical evaluation too1 for both clinical and research purposes for the Dutch population group during brace treatment. Lastly, a general discussion is presented in **Chapter 8**, in which also future perspectives regarding this thesis research field will be discussed.

Nederlandse samenvatting

Idiopathische scoliose is een complexe driedimensionale (3D) deformiteit van de wervelkolom, die zich onder andere kenmerkt door een zijdelingse verkromming van ten minste 10 graden en een verdraaiing om zijn eigen as. De term scoliose komt van het Griekse woord ‘skoliosis’ dat ‘krom’ betekent, en de term ‘idiopathisch’ omvat alle patiënten waarbij geen onderliggende oorzaak is gevonden voor de deformiteit. Idiopathische scoliose is veruit de meest voorkomende vorm van scoliose, en wordt bij ongeveer 3 op de 100 kinderen onder de 16 jaar vastgesteld. De meeste kinderen met deze vorm presenteren zich vaak na hun 10^{e} levensjaar tijdens de adolescente groeispurt, en hun scoliose wordt daardoor ook wel geclassificeerd als adolescente idiopathische scoliose (AIS). Wanneer je de scoliose niet behandelt, bestaat er het risico op een verergering van de bocht. Deze verergering, ook wel progressie genoemd, kan leiden tot ernstige romp deformiteiten met longproblemen, cosmetische problemen, pijn, progressieve functionele beperkingen en verminderde kwaliteit van leven (KvL). Daarom worden de ernstige zijwaartse scoliosebochten met een hoek van meer dan 45-50 graden meestal chirurgisch behandeld. Om een chirurgische behandeling te voorkomen, worden patiënten met kleinere bochten met een brace behandeld tijdens hun adolescente groeispurt, met als doel de bocht onder de 45 graden te houden. Een bracebehandeling is echter niet succesvol bij elke patient en er is ruimte voor verdere verbeteringen. Het doel van dit proefschrift was om de mogelijkheden te onderzoeken voor het gebruik van biplanaire röntgenfoto’s met lage dosis straling voor wervelkolom gerelateerde metingen, en om verdere verheldering te verkrijgen omtrent factoren die geassocieerd zijn met een succesvolle bracebehandeling bij AIS.

Deel 1. Adolescente idiopathische scoliose

Het eerste deel van dit proefschrift focust zich op de validatie van de wervelkolomlengte en de grootte van het boogvoetje (pedikel) van de wervel op röntgenfoto’s die gegenereerd zijn met een biplanaire röntgenapparaat met lage dosis straling (EOS® beeldvorming, Parijs, Frankrijk). Deze EOS röntgenfoto’s gebruiken substantieel minder straling dan Computer Tomografie (CT-scan) en conventionele röntgenfoto’s, hebben geen divergentie in het verticale vlak, en geven de mogelijkheid om 3D metingen uit te voeren met behulp van de EOS beeldvorming software. In **Hoofdstuk 2** worden de validatie en betrouwbaarheid van EOS tweedimensionale (2D) en 3D wervelkolomlengtemetingen in patiënten met AIS onderzocht. Kennis over de wervelkolomlengte, en vervolgens ook de groei van elke AIS-patiënt, helpt namelijk met het nauwkeuring plannen van zowel de niet-operatieve als operatieve behandeling. Voorafgaand aan de routine EOS röntgenfoto, werd een radiografische, gekalibreerde, metalen kralensnoer met tape vastgeplakt op de huid over de doornuitsteeksels van de wervelkolom bij 50 geïncludeerde AIS patiënten om de beelden te kalibreren. Met behulp van de EOS software konden zowel 2D als 3D wervelkolomlengtemetingen gedaan worden, die vervolgens vergeleken werden met de kralensnoermetingen. Er werd een goede validiteit en betrouwbaarheid gevonden voor de totale, thoracale, lumbale en segmentale wervelkolomlengtemetingen op EOS röntgenfoto's. In tegenstelling tot de 3D metingen, onderschatten de 2D metingen op het aparte coronale of sagittale vlak van de röntgenfoto structureel de wervelkolomlengte. Dit is niet heel verrassend aangezien de deviaties in het andere vlak niet meegenomen zijn tijdens 2D metingen van een complexe 3D deformiteit van de wervelkolom. Wanneer de EOS 3D meetmethode niet mogelijk is, zouden de 2D wervelkolomlengtemetingen op het sagittale vlak de voorkeur hebben boven metingen op het coronale vlak bij zijwaartse scoliosebochten met een hoek onder de 40 graden.

In **Hoofdstuk 3** werd de toepassing van het EOS röntgenapparaat voor wervelkolom gerelateerde metingen verder onderzocht. In deze studie werden de intra- en extracorticale pedikelhoogte- en pedikelbreedtemetingen op preoperatieve, coronale EOS röntgenfoto's vergeleken met gereconstrueerde intra-operatieve 3D-beelden van het nauwste deel, de isthmus, van 203 geïncludeerde pedikels van geopereerde patiënten. Er werd een goede validiteit en een uitstekende relatieve interbeoordelaars- en intrabeoordelaarsbetrouwbaarheid voor pedikelgrootte metingen op EOS röntgenfoto's gevonden, waardoor chirurgen die uit de vrije hand pedikelschroeven inbrengen preoperatief betrouwbaar de intra- en extracorticale pedikel breedtes op EOS röntgenfoto's kunnen meten voor een indicatie van de benodigde schroefdiameters voor die specifieke pedikels. Goede formaat pedikelschroeven dragen bij aan een goede houvast in het bot en verkleinen de kans op een pedikelbreuk. Chirurgen zouden echter rekening moeten houden met een kleine (0,47mm), maar klinisch waarschijnlijk irrelevante, systematische onderschatting van de pedikelbreedtemetingen op EOS röntgenfoto's bij het meten van zichtbare pedikels van geroteerde wervels.

Deel 2. Bracebehandeling

Het tweede gedeelte van dit proefschrift focust zich op de bracebehandeling als niet-operatieve behandeling van AIS. Een bracebehandeling tijdens de adolescente groeispurt verkleint significant de kans op progressie en daarmee ook de kans op een operatieve correctie. Echter, deze behandeling is niet succesvol bij elke patiënt, en er is sterk bewijs gevonden voor de associatie tussen het gebrek aan een goede eerste correctie van de scoliosebocht in de brace (initiële in-brace correctie) en de kans op het falen van de bracebehandeling. Voortbordurend hierop is in **Hoofdstuk 4** een systematische review met een beste bewijs synthese verricht, die kijkt naar voorspellende factoren voor de mate van initiële in-brace correctie bij patiënten met idiopathische scoliose. . Vierendertig verschillende genoemde factoren waren verzameld uit 28 geïncludeerde studies, waarvan 9 studies (32%) geclassificeerd werden als een hoge kwaliteit studie. Er was sterk bewijs gevonden voor toegenomen flexibiliteit van de scoliosebocht, en matig bewijs voor thoracolumbale of lumbale bochten als gunstige factoren voor een betere initiële in-brace correctie. Ook was er matig bewijs gevonden voor een scoliose patroon met een dubbele grote bocht als ongunstige factor, en dat braces die ontworpen zijn met computer ontwerp- en fabricagesystemen met of zonder Finite Element Analysis niet tot een significant betere initiële in-brace correctie leiden ten opzichte van braces die gefabriceerd zijn met de conventionele gipsmethode. In tegenstelling tot de type scoliose en flexibiliteit zijn brace ontwerp- en fabricagetechnologieën factoren die theoretisch gezien verder ontwikkeld kunnen worden door de medisch instrumentenmaker. Computerontwerpsystemen kunnen bijvoorbeeld gebruikt worden om de romp van een patiënt in drie dimensies en bracekarakteristieken te kwantificeren. In **Hoofdstuk 5** wordt een pilotstudie beschreven over 25 AIS-patiënten waarbij de mate van torso-asymmetrie en segmentale positieve en negatieve piek-torsoverplaatsingen geanalyseerd zijn met behulp van de 3D oppervlaktescans van patiënten en bracemodellen voor een potentiële correlatie met initiële in-brace correctie. De algemene resultaten van deze pilotstudie suggereren echter dat voor Lenke type 1 en 5 bochten zowel de mate van torso-asymmetrie als segmentale piek-torsoverplaatsingen in het bracemodel alleen niet duidelijk geassocieerd zijn met initiële in-brace correctie. Harde conclusies kunnen op basis van deze pilotstudie echter niet worden getrokken, waardoor er meer onderzoek nodig is naar factoren die bijdragen aan het voorspellen en verder verbeteren van de initiële in-brace correctie.

Naast initiële in-brace correctie speelt therapietrouw ook een essentiële rol in het succes van een bracebehandeling. Om de therapietrouw tijdens de bracebehandeling te verbeteren, zou een vroege detectie van progressie van de scoliosebocht belangrijk kunnen zijn omwille van motivatieredenen, want de wens van patiënt om progressie te voorkomen en chirurgische behandeling te vermijden zijn als de meest belangrijke positieve factoren die invloed hebben op de therapietrouw beschreven. In **Hoofdstuk 6** wordt een retrospectieve studie beschreven die twee gestandaardiseerde protocollen voor radiologische follow-up (in-brace versus uit-brace röntgenfoto's) uit twee scoliosecentrums op progressiesnelheid vergelijkt bij 51 chirurgisch behandelde patiënten met idiopathische scoliose na een gefaalde bracebehandeling.

De gemiddelde follow-up duur van de studie was 3.4 jaar, en de snelheid waarmee progressie van de scoliosebocht optrad was vergelijkbaar wanneer patiënten met de in-brace of uit-brace radiologische follow-up protocol vervolgd werden. De snelheid bedroeg ongeveer 0.5 graden per maand in beide groepen. In de dagelijkse praktijk kunnen in-brace follow-up röntgenfoto's daarom overwogen worden voor patiënten met relatief kleine bochten om ook de in-brace correctie te kunnen beoordelen zodat er zo nodig aanpassingen aan de brace gedaan kunnen worden. Maar voor de potentiële kandidaten voor een chirurgische behandeling met de grotere scoliosebochten zou het protocol met uit-brace röntgenfoto's of een switch van in-brace naar uit-brace follow-up protocol de voorkeur hebben, omdat uit-brace röntgenfoto's meer informatie kunnen verschaffen voor de klinische besluitvorming.

Een andere benadering die tot nieuwe inzichten voor een betere therapietrouw tijdens de bracebehandeling kunnen leiden, is om eerst meer kennis te verkrijgen omtrent de impact van het dragen van een brace en het effect van nieuwe brace-aanpassingen of brace gerelateerde interventies op verschillende KvL-domeinen. Dit kan echter niet gedaan worden in Nederland zonder een ziekte-specifieke gezondheid gerelateerde KvL meetinstrument voor de Nederlandse scoliosepatiënten die bracetherapie ondergaan. Om deze reden wordt er in **Hoofdstuk 7** de validiteit en betrouwbaarheid van een vertaalde en cultureel aangepaste Nederlandse versie van de Brace Vragenlijst onderzocht. Na een zorgvuldige vertaling van de Brace Vragenlijst vanuit het Grieks, laat de Nederlandse versie van de vragenlijst een goede validiteit en betrouwbaarheid zien. Ook zijn de uitkomsten van de studie vergelijkbaar met de literatuur, waardoor de Nederlandse versie van de Brace Vragenlijst gebruikt kan worden als een betrouwbaar meetinstrument voor zowel klinische als onderzoeksdoeleinden voor de Nederlandse populatiegroep tijdens de bracebehandeling.

Tenslotte wordt in **Hoofdstuk 8** een algemene discussie gepresenteerd, waarin ook toekomstperspectieven betreffende het onderzoeksveld van dit proefschrift besproken worden.

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Dankwoord

"We must find time to stop and thank the people who make a difference in our lives" – John. F. Kennedy.

Dankbaarheid is een van de belangrijkste dingen in de wereld. Zo hebben mijn vrouw en ik de gewoonte om wekelijks één ding te benoemen waar we op dat moment dankbaar voor zijn. Soms gaat dat gepaard met een knipoog of een grap, maar meestal komen er ook mooie bewustwordingen uit voort. Het is vanzelfsprekend dat ik dit proefschrift niet alleen heb kunnen volbrengen. Daarom wil ik een aantal personen in het bijzonder bedanken voor hun waardevolle bijdrage aan dit proefschrift.

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About the author

Carlo Peeters was born on June 13th, 1990 and was raised on a farm in a small village named Dorst, together with his three sisters. After his graduation from secondary school in 2008 (Gymnasium, Stedelijk Gymnasium Breda), he started his medical training at Erasmus University Rotterdam. In 2017 he started his general surgery training at Deventer hospital under the supervision of Dr. B.H.P. Elsman, followed by his residency in orthopaedic surgery at UMCG (supervision: prof. dr. S.K. Bulstra & prof. dr. P.C. Jutte), Deventer hospital (supervision: dr. J.P.W. van Jonbergen & dr. C.T. Koorevaar), and Isala (supervision: dr. R.G. Zuurmond). During his period at UMCG he initiated his PhD trajectory under the supervision of Prof. dr. P.C. Jutte, dr. C. Faber, dr. F.H. Wapstra and dr. D.H.R. Kempen. Carlo completed most of his studies in his last three years of training at Isala, where he will finish his residency in 2024. In his spare time, Carlo has written several books for children, two for the age 8-10, and three for beginning readers of the age 6-7. In 2021 his daughter Linde was born and on weekends he loves spending time with his family, in particularly outdoors to enjoy the nature, culture and leisure.

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Part 3: Bram is boos (2022)

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Publisher: Eigenzinnig
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2020: **Second edition of "Donderslag"**
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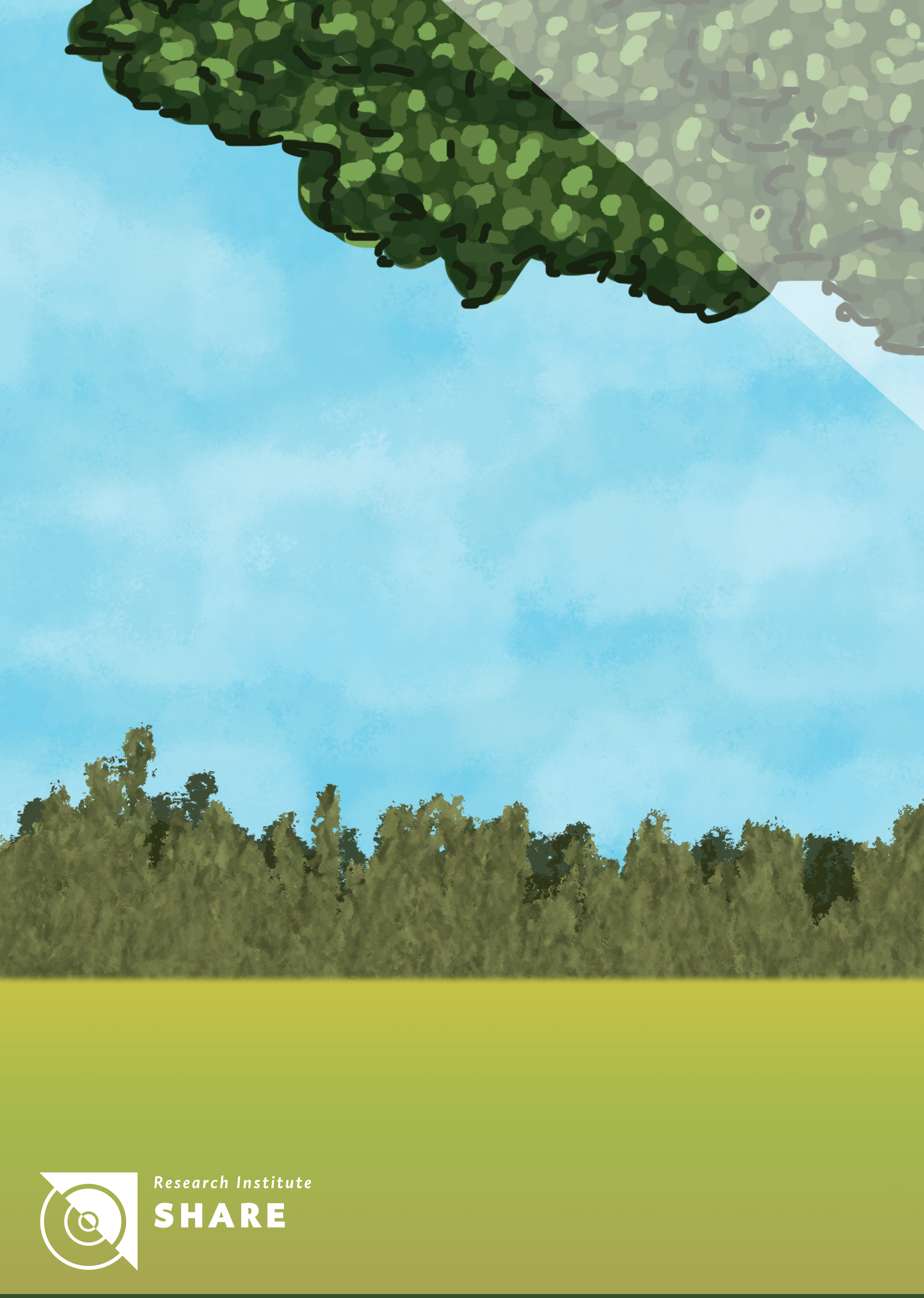

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