Adolescent Idiopathic Scoliosis

From Normal Spinal Anatomy To Three-Dimensional Deformity

Tom P.C. Schlösser

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PhD thesis, Utrecht University

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Adolescent Idiopathic Scoliosis:
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Adolescente Idiopathische Scoliose:
Van Normale Spinale Anatomie naar Driedimensionale Deformiteit

(met een samenvatting in het Nederlands)

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geboren op 25 mei 1987 te Heerlen

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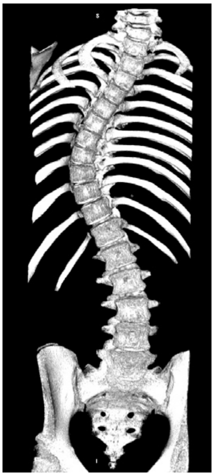
Chapter 1

Introduction, Aims and Outline of this thesis



Scoliosis is a three-dimensional (3-D) deformity of the spine and trunk that primarily affects previously healthy children. It is a classic orthopedic disorder.[1] The most common type of scoliosis is *idiopathic* scoliosis. The term 'idiopathic' (from the Greek: ίδιος=one's own and πάθος=suffering) is meant to imply that the disease is not linked to any physical impairment or previous medical history. Despite many years of dedicated research into the etio-pathogenesis of idiopathic scoliosis, there is not one distinct cause for this condition and its etiology is called multifactorial.[2]

At present, no adequate causal treatment or preventive measures are available. So, treatment is instituted when the deformity is already rather pronounced and relies to a large extent on aggressive non-surgical and surgical means. Apart from the impact of the spinal deformity on quality of life, scoliosis patients are also a considerable economic burden to society: idiopathic scoliosis affects approximately 2-3 percent of the population, about six million people in the United States, it is the spinal deformity most frequently seen by general practitioners, pediatricians and orthopedic surgeons, and current therapies are very costly.[3, 4]

It has been shown that the unique, fully upright spinal biomechanics of man plays an important role in the initiation and progression of idiopathic scoliosis.[5-8] This disorder is related exclusively to humans, it has not been observed in any other mammalian.[9] Other spinal deformities have been observed or created in animals, but they either have iatrogenic, post-traumatic, neuromuscular or congenital etiologies. The fully upright human posture and bipedal ambulation differs considerably from that of other, quadrupedal as well as bipedal, species. As a result, the way the upright human spine is biomechanically loaded, with its consequences for the delicate balance between different loads that act on the spine and the bodies compensating mechanisms and subsequent impact on stability of certain spinal segments, is a unique feature of man.[5, 7, 8]

THE NORMAL SPINE

Sagittal spino-pelvic alignment in human evolution

The essential difference between man and all other vertebrates is not any major difference in spinal architecture. This is relatively uniform throughout all species with broad vertebral endplates and discs to withstand axial loading, and posteriorly located synovial joints and protuberances for muscle and ligament attachment to withstand anteriorly directed shear loads (figure 1). Humans, however, have a unique combination of fully upright sagittal spino-pelvic alignment and fully upright bipedal ambulation. Due to this configuration, *Homo sapiens* is the only species that can simultaneously

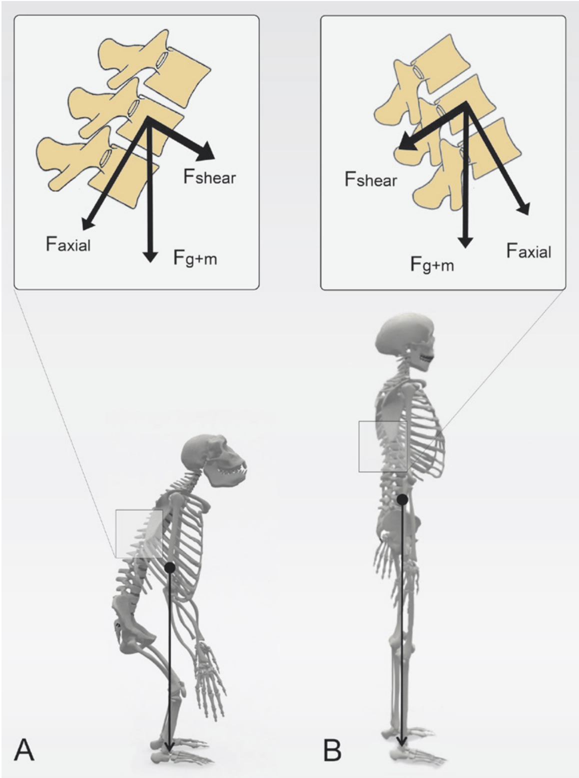


Figure 1. Anteriorly inclined vertebrae are affected by an axial force and anteriorly directed shear force, whereas posteriorly inclined vertebrae are affected by posteriorly directed shear force. The amount of each depends on an individual's sagittal spinal profile (data compiled from Kouwenhoven et al.[6] and Janssen et al.[7]).

extend both hips as well as knees, putting the body's center of gravity straight above the pelvis. In contrast, Bonobo's, human's closest relative, consistently ambulate with a flexion contracture of the hip and knee, and a center of gravity in front of the pelvis. This poses unique loads on the human spine that have been shown to lead to a reduction of rotational stiffness of certain exposed segments (figure 1).[5-8] Human sagittal spino-pelvic alignment in combination with habitual bipedalism is therefore unique, cannot be found in any other mammalian and introduces unique spinal biomechanics.

It is generally accepted by anthropologists that human habitual bipedalism, i.e. fully upright locomotion with extended hips and knees, as well as sagittal spino-pelvic alignment can be attributed to the morphological changes of the pelvis in human evolution.[10, 11] In the earliest hominid specimen to date, an *Australopithecus afarensis* that was found in Ethiopia (also known as 'Lucy'), as well as in other hominids, anthropologists observed that angulation of the ilium relative to the ischium, enabled upright human

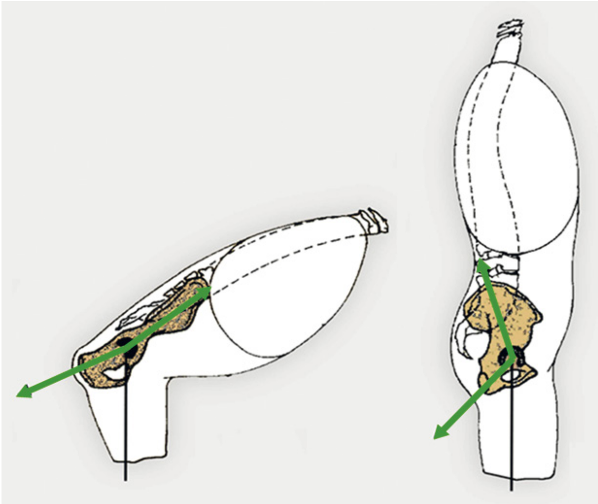


Figure 2. On the left side the relatively small ischio-iliac lordosis and sagittal spinal profile is illustrated for a non-human primate, on the right the ischio-iliac lordosis and sagittal spinal profile for an upright human spine (data compiled from Kummer[60, 61]).

locomotion.[12] Even in human's closest relatives, the bonobo's and chimpanzees, there is almost no angulation between the ischium and ilium. When a primate tries to stand upright, the trunk simply swings up on the femoral heads to a point that the ischium points almost directly downward. The ischium, however, is the lever arm for the ischio-femoral muscles and plays an important role in the extension of the hips. In a primate in upright position, the ischium points straight down and the hip extensors have run out of power by the time the femoral shaft is vertical. For occasional bipedal locomotion, primates need to bend their knees and hips, which positions the center of mass of the upper body in front of the pelvis.[13] For energy-efficient human bipedal locomotion, however, lordotic angulation of the ilium relative to the ischium was a prerequisite to be able to walk fully upright (figure 2).[10, 14, 15]

The role of the pelvis in sagittal spinal balance

In 1992, Duval-Beaupère et al. demonstrated the importance of the pelvis as a key regulator of sagittal spino-pelvic balance. They introduced the pelvic incidence as a parameter for sagittal pelvic morphology and pelvic tilt and sacral slope for sagittal pelvic orientation. In this sense, pelvic morphology refers to the position of the sacral plate within the pelvic ring and is not position dependent, whereas pelvic orientation is adaptive and depends on its configuration in space.[16] Recently, Mac-Thiong et al. demonstrated that, by anteflexion and retroflection, the pelvis is a key regulator of sagittal configuration of the sagittal contour of the lumbar, thoracic and cervical spine in order to keep the center of mass of the body and the head straight above the femoral heads.[17, 18]

Biomechanical consequences of sagittal spino-pelvic alignment

Variation in sagittal alignment of the spine is increasingly recognized in relation to normal functioning, and in the etio-pathogenesis of spinal deformities. Although all spines in nature are predominantly loaded in an axial direction, the orientation in space of each individual vertebra determines whether it is, in addition to axial loading, subject to either anteriorly-directed or posteriorly-directed shear loading as a result of gravity and muscle tone (figure 1).[5, 7] Vialle et al. and Roussouly et al. have shown that an excess of anterior shear, under certain circumstances, can lead to anterior displacement of the vertebral body, known as spondylolisthesis.[19-21] Previous work by Vercauteren in 1980 and Castelein et al. in 2005 has clarified that a certain area of the human spine in the upright position is posteriorly inclined and affected by posteriorly directed shear loads.[5, 7, 22] From this perspective, Janssen et al. showed that posterior shear loads act on all posteriorly inclined segments of the spine as determined by each individual's sagittal profile.[7, 23] In an experimental setup, Kouwenhoven et al. have shown that an excess of posterior shear loads results in diminished rotational stiffness of spinal segments.[6] Therefore, the more the spine exhibits areas with posteriorly tilted vertebrae, the more these segments are prone to develop a rotational deformity, in other words scoliosis.[5, 8]

Pre-existent rotation of the normal spine

As has been appreciated for a long time, the normal spine is not a symmetrical structure.[24] In 2006, Kouwenhoven et al. demonstrated the presence of an axial rotational pattern in the normal human spine, that is similar to what is seen in the most prevalent curve patterns in idiopathic scoliosis.[25, 26] In addition, in a study on the effect of body position on the rotation of the normal spine, it was observed that the pre-existent rotational patterns were less pronounced if non-scoliotic humans assumed a quadrupedal position, in comparison with the supine and upright positions.[26-28]

IDIOPATHIC SCOLIOSIS

Classification of (idiopathic) scoliosis

Scoliosis can be the result of a neuromuscular disorder (neuromuscular scoliosis), can be attributed to a congenital anomaly of the spine (congenital scoliosis), one of the manifestation of a syndrome with skeletal or connective tissue abnormalities (syndromic scoliosis) or can be a symptom of leg-length discrepancy (functional scoliosis). Idiopathic scoliosis, however, has no known cause. It can occur in young children during the infantile growth spurt or at the juvenile age, but in 90% of the cases initiation and progression of idiopathic scoliosis takes place around the adolescent growth spurt. Based on the age of onset of the deformity, it can be subdivided into infantile (0-3 years old), juvenile (4-9 years old) and adolescent idiopathic scoliosis (AIS) (10-16 years old), or in early-onset (0-9 years old) and late-onset idiopathic scoliosis (10 years or older).[29] Some of the unexplained, but well known–characteristics of pediatric spinal deformities are that they normally develop and progress around the pubertal growth spurt, and that girls are far more often affected by AIS, whereas boys are more often affected by Scheuermann's kyphosis.[30, 31] Moreover, while in infantile idiopathic scoliosis, boys are affected more often than girls and curves are typically left-convex, in adolescent idiopathic scoliosis, predominantly girls are affected and curves are typically right-convex.[3]

Morphology and curve types in adolescent idiopathic scoliosis

The Scoliosis Research Society defines scoliosis as a lateral curvature of the spine of more than 10 degrees in the coronal plane.[32] This formal definition denies the fact that it is actually a complex 3-D spinal deformity. Already in the late nineteenth and early twentieth century, using cadaver specimens, anatomists carefully described that adolescent idiopathic scoliosis involves changes in the coronal, transverse as well as the sagittal plane.[1, 33] In the coronal plane it is characterized by lateral deviation and lateral bending, in the transverse plane by axial rotation, asymmetrical growth of the pedicles and asymmetrical closure of the neurocentral cartilages and in the sagittal plane by lordosis of the apical segments and hypertrophy of the facet joints. A typical feature of the curves in AIS is the coupling between the phenomena in the three different planes. In 1952, Somerville and Roaf described that during the development of AIS the vertebral bodies rotate away from the midline toward the convexity, to a more lateral position than the posterior elements of the spine.[34, 35] By definition, axial rotation towards the convexity of the curve leads to a spinal column that is latero-flexed and is longer anteriorly than posteriorly, in other words, rotated lordosis of the apex. Because of the rotated apical lordoses in AIS, Stagnara introduced *le plan d'election*, a rotated view to evaluate the true coronal profile of the apical segments of the curvature.[36] Using this view, in 1984 Dickson et al. observed in 70 AIS patients that instead of a normal thoracic kyphosis, 75% of the AIS curves were lordotic, 24% were straight and only 1% kyphotic.[37, 38] In this thesis, a detailed 3-D study of the different curves and junctional zones is meant to shed more light on this issue.

Scoliotic curves can be classified according to location, severity and rigidity. In AIS generally three curves can be found: a high thoracic, a main thoracic and a (thoraco)lumbar curve. Normally, the initiation of deformation starts in one area of the spine, the primary curve. In order to maintain a well-balanced spine with the head straight above the pelvis, secondary curves, also known as compensatory curves, can develop. The most widely used method for estimation of the size of a scoliotic curve is by measurement of the Cobb angle on two-dimensional anterior-posterior radiographs (figure 3).[39] In 1983, King

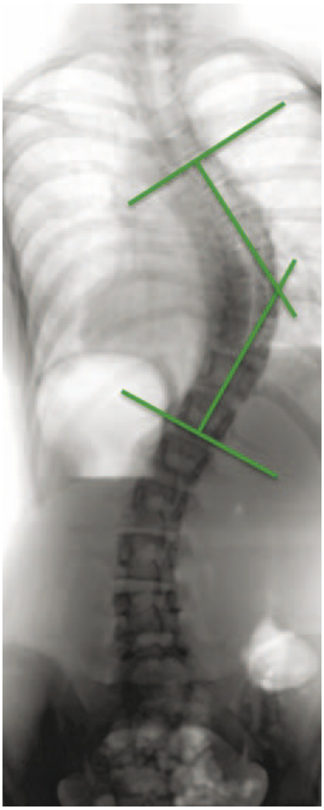


Figure 3. Cobb angle measurement of the coronal plane deformity on an anterior-posterior radiograph of a 14-year old girl with adolescent idiopathic scoliosis.

et al. introduced a classification system based on the location and severity of the coronal deformity.[40] In 2001, Lenke et al. introduced a classification system including the curve types in the coronal plane, the alignment in the sagittal plane as well as the rigidity of the curves on lateral bending radiographs.[41] Each primary and secondary curve will carry a certain amount of rigidity on those radiographs. Lateral bending radiographs are often acquired to assess the rigidity of the curves. If the deformity significantly improves when the patient actively bends to the concave side of the curve, it means the curve is less rigid and can be straightened during scoliosis surgery without aggressive osteotomies. In general, with progression of the deformity, there is loss of flexibility. According to Lenke et al., curves more than 25 degrees on the bending radiographs are called 'structural' and curves equal to or less than 25 degrees 'non-structural'. The most prevalent AIS curve types are primary, right-sided main thoracic curves (Lenke 1 and 2).[41, 42] In the near future, accurate 3-D classifications of scoliosis may become available as a result of the introduction of innovative imaging techniques, such as biplanar radiography, low-dose computed tomography and upright magnetic resonance imaging.[43, 44]

Natural history of untreated AIS

Progression of the deformity depends on skeletal maturity of the patient and the magnitude of the spinal curvature. AIS is the most prevalent type of idiopathic scoliosis and implies a more benign course than infantile or juvenile idiopathic scoliosis. In addition to progression during childhood, Nachemson showed that the magnitude of AIS curves tends to increase over the entire life, but the speed of progression drops after skeletal maturity.[45] In terms of severity, sixty percent of the curves between twenty and twenty-nine degrees diagnosed at an age of ten to twelve years old will progress during later life, whereas approximately 100% of the curve greater than forty degrees will further progress. Early long-term studies in the 1970s, 1980s and 1990s showed that, if a severe progressive AIS curve is left untreated it has a poor prognosis: it could lead to severe deformation of the spinal column and the complete rib cage, restricting the area of the lungs with shortness of breath and sometimes debilitating pain.[46-48] These studies, however, included subjects with mixed diagnoses. In more modern prospective long-term studies of Weinstein et al. and Asher et al., most untreated AIS patients had comparable or slightly increased back pain or cardiopulmonary compromise at 20 to 50 year follow-up as compared to their peers.[49, 50] In general, they were less satisfied with their body image than controls, sometimes leading to psychological distress and a negative impact on quality of life (figure 4).[50]

Figure 4. A photography of a skeleton with severe scoliosis demonstrating that the area of the lungs is severely restricted due to rib deformations.

Treatment of AIS

Treatment of AIS attempts to alter the natural history of the disease. The most common non-operative management for AIS are regular clinical and radiological examinations and conservative brace treatment. Bracing, however, is only effective in rapidly growing immature patients with a mild spinal curvature (10-29 degrees).[51] Moreover, braces can be uncomfortable for patients, they can pose a psychological burden and the ultimate result can be disappointing. Operative treatment does not completely cure scoliosis, but helps to correct and manage curve progression to prevent further deformation and attempts to restore balance. Furthermore, there is evidence that successful restoration of coronal and sagittal balance may have a protective effect on the unfused discs.[52] In general, scoliosis surgery is indicated for curves over 45 degrees Cobb angle. If no further growth is expected, posterior or anterior spinal fusions can be performed. A fusionless, growth-sparing technique is an option for immature children, but this is not a definitive treatment. The basic principle for definitive AIS surgery implies that the deformity is corrected in all three-dimensions, and the spine is fused in an optimally balanced configuration in all three planes.

OUTLINE AND QUESTIONS TO BE ADDRESSED IN THIS THESIS

The overall aim of this thesis is to determine intrinsic factors in human spinal upright biomechanics that play a role in the initiation and progression of adolescent idiopathic scoliosis. Ultimately, a better understanding of the true nature of the disorder, and the factors that contribute to its initiation and progression, should lead to more rational, less invasive and costly as well as preventive measures in the future. This thesis is divided into two sections of a number of imaging studies, a biomechanical and a clinical investigation: in part 1, spino-pelvic morphology of nonscoliotic human subjects is characterized. Part 2 aims at further exploration of the biomechanical mechanisms in progression of AIS. Also, in this part, the true three-dimensional anatomy of scoliosis is described in detail, and consequences for surgical correction are addressed. An internationally used Patient Related Outcome Measure (PROM) is validated for the Dutch language. In this thesis a number of questions are explored.

As referred to above, although the term 'idiopathic' implies that the patient is otherwise -except for the spinal deformity- normal, many subtle or subclinical extra-spinal abnormalities of AIS patients have been reported in the literature. Frequently, it has been suggested that these findings are related to the etiology of the disorder. In **Chapter 2** we performed an extensive systematic review of the reported concomitant abnormalities. The characteristics and relevance of various abnormalities for the etio-pathogenesis are discussed. This leads to the following research question:

I. What abnormalities exist in AIS patients as compared to healthy adolescents, and could these play a role in the etio-pathogenesis (chapter 2)?

Some of the unexplained, but well known characteristics of pediatric spinal deformities are that they normally develop and progress around the pubertal growth spurt, and that girls are far more often affected by AIS.[30] From previous studies, it can be inferred that, due to biomechanical forces that act on the posteriorly inclined area of the spine, certain sagittal spinal profiles are more prone to develop a rotational deformity than others.[5, 8, 26] In order to understand the typical timing of the onset of acquired spinal deformity at the adolescent age, the development of the sagittal spinal profile during the normal phases of the adolescent growth spurt was investigated in **chapter 3**.

II. What is the natural development of sagittal spino-pelvic alignment during the adolescent growth spurt (chapter 3)?

The role of the pelvis, as a controller for spinal alignment and keeping the spine optimally balanced, is becoming increasingly apparent.[16] In the field of anthropology, the development of a lordosis between the ischium and ilium was the crucial step forward for human bipedalism and distinguishes humans from all other mammalians.[10] The morphological changes in the pelvis, including the lordotic angulation between the ischium and ilium, have never been quantified in a growing population. In **chapter 4** we assessed sagittal pelvic morphology on 3-D computed tomography scans of normal children and adults.

III. What is the influence of growth and aging on sagittal pelvic morphology? (chapter 4)?

In previous studies, we have shown that the pre-existent axial rotational pattern of the normal, nonscoliotic adult spine corresponds to the pattern of rotation and convexity of the curve in adolescent idiopathic scoliosis.[25] The convexity of the curve in AIS, however, differs significantly from infantile and juvenile idiopathic scoliosis. To test the hypothesis that rotation and the convexity of the curve in idiopathic scoliosis follows the pre-existent rotational pattern of the normal spine, we investigated the pre-existent rotation of the normal pediatric spine at the infantile, juvenile and adolescent age in **chapter 5**.

IV. What are the pre-existent rotational patterns of the normal pediatric spine (chapter 5)?

The neurocentral junctions of the vertebrae connect the pedicles and laminae to the vertebral body bilaterally, and allow for growth in radial direction of the spinal canal. In the literature, it has been proposed that asymmetrical growth in the neurocentral junctions (also known as neurocentral synchondroses or cartilages) of the vertebral bodies could result in asymmetrical pedicle growth, axial vertebral rotation and a rotational spinal deformity.[53, 54] Other investigators, however, showed that the neurocentral cartilages are active at the infantile and juvenile age, but are already closed at the adolescent age.[55] We hypothesize that asymmetrical growth of the neurocentral junctions is not necessarily related to the etiology of scoliosis, but may play an essential role in the development of pre-existent axial rotation of the spine and the convexity of the curve in idiopathic scoliosis. In **chapter 6** we present a study in which the closure of the neurocentral junctions was investigated on computed tomographic scans of asymptomatic children at different ages in relation to pre-existent rotation of the spine.

V. Do the pre-existent rotational patterns of the pediatric spine correspond to asymmetrical closure of the neurocentral junctions (chapter 6)?

It has previously been shown that rotational stiffness of spinal segments is decreased by posteriorly directed shear loads.[6] Posterior shear loads act on backwardly inclined segments of the spine as determined by the individual's inherited sagittal spinal profile. Accordingly, in **chapter 7** we hypothesized that typical thoracic AIS, on the one end of the spectrum, develops on a different sagittal spinal profile than typical lumbar AIS on the other end.

VI. What is the difference in sagittal spino-pelvic alignment between thoracic and lumbar adolescent idiopathic scoliosis at an early stage (chapter 7)?

The fact that idiopathic scoliosis is a complex 3-D deformity of the spine, rather than a simple lateral curvature, has been well appreciated for a long time.[1] The true 3-D morphology of the different areas of the scoliotic spine, however, has not been described in detail to date. The debate about the etio-pathogenesis of the disorder continues and modern day surgical techniques aim at restoring normal anatomy in all three planes as closely as possible. Both considerations require accurate knowledge of the exact nature of the disorder. For this reason, in **chapter 8**, the true 3-D regional morphology of the individual curves and junctional segments in different types of AIS were studied and compared to normal anatomy, using high-resolution computed tomography scans from Hong Kong as well as Utrecht.

VII. What is the true 3-D morphology of adolescent idiopathic scoliosis (chapter 8)?

There is an ongoing debate on the development of the excess of anterior spinal length in AIS. Because the spinal column in AIS, unlike the normal situation, is longer anteriorly than posteriorly, it has been hypothesized that AIS is the result of active anterior overgrowth of the vertebral bodies, or reduced posterior growth by posterior tethering.[56, 57] From our etiological perspective, however, the anterior-posterior length discrepancy in

AIS is secondary to axial rotation. In **chapter 9**, we investigated whether the 3-D deformation of the spine is predominantly localized in the vertebral bodies (as a result of active growth) or the discs (as a secondary phenomenon to axial rotation).

VIII. Where is the 3-D deformity in adolescent idiopathic scoliosis localized, in the discs or vertebral bodies (chapter 9)?

Knowing the true 3-D anatomy of scoliosis, the question was raised how an optimally balanced correction can best be achieved. Multilevel posterior releases, or Ponte osteotomies, are used in scoliosis surgery in order to facilitate correction of axial rotation and to restore normal sagittal alignment.[58] These releases involve removing the facet joints and posterior spinal ligaments. However, it is unclear how much release of posterior structures is required for an optimal surgical result. The goal of the study in **chapter 10** was to quantify the contribution of each subsequent step in the spinal release on thoracic spinal motion, in order to quantify how extensive a posterior release is necessary in AIS corrective surgery.

IX. What effect do multilevel posterior releases have on spinal mobility (chapter 10)?

Even without severe progression, when the curves are usually not life threatening and no brace or surgical treatment is used, AIS may interfere with daily life and have significant effects on quality of life. Moreover, the effectiveness of current scoliosis treatment on health related quality of life is not very well described. The introduction of patient recorded outcome measures enables a comprehensive evaluation of the patient's perspective on the disease and the efficacy of both conservative and invasive surgical treatments.[59] In the field of scoliosis, the (revised) Scoliosis Research Society 22-item questionnaires gained wide acceptance globally and have already been translated into seventeen different languages. In **chapter 11** the Dutch validation of the SRS-22r is presented, because there is a great need from the clinical as well as research perspective.

X. Can we translate and adapt the revised Scoliosis Research Society 22-item questionnaire for the Netherlands (chapter 11)?

In **chapter 12**, results of the chapters are summarized and discussed; answers to the questions are provided followed by a final conclusion.

Chapter 2

How 'Idiopathic' is Adolescent Idiopathic Scoliosis? A Systematic Review on Associated Abnormalities

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ABSTRACT

Purpose. Despite more than a century of dedicated research, the etiology and pathogenesis of adolescent idiopathic scoliosis (AIS) remain unclear. By definition, 'idiopathic' implies an unknown cause. Nevertheless, many abnormalities concomitant to AIS have been described, often with the suggestion that these abnormalities are related to etiopathogenesis. Insight in the concomitant abnormalities may assist in improving the understanding of the etiological pathways of AIS. We aimed to systematically review and synthesize available studies on abnormalities concomitant to AIS.

Methods. Original studies comparing untreated AIS patients with healthy adolescents on abnormalities other than the deformity of the spine were retrieved from PubMed and Embase. We followed PRISMA guidelines and to quantify the relationship between each abnormality and AIS we used a best-evidence-syntheses for relating risk-of-bias to consistency of effect sizes.

Results. We identified 88 relevant citations, forty-seven carried high risk-of-bias and twenty studies did not report quantitative data in a sufficient manner. The remaining twenty-one publications failed to report data from before initiation of the deformity and blind assessments. These cross-sectional studies provided data on fourteen abnormalities concomitant to AIS. With our best-evidence-syntheses we were unable to find both strong evidence and a consistent pattern of occurrence for AIS and any of these abnormalities. From moderate risk-of-bias studies a relatively consistent pattern of occurrence for AIS and impaired gait control (4 studies; 155 subjects; Cohen's d= 1.00) and decreased bone mineral density (2 studies; 954 subjects; Cohen's d= −0.83) was found. For nine abnormalities a consistent pattern of occurrence with AIS was found, but the evidence for these was weak.

Conclusions. Based on the available literature, strong evidence is lacking for a consistent pattern of occurrence of AIS and any abnormality. The relevance for understanding the multifactorial etiology of AIS is very limited.

INTRODUCTION

Scoliosis is a complex three-dimensional deformity of the spine.[1] Although there are many forms of scoliosis, most cases (84-89%) develop without a known cause, in previously healthy girls during the adolescent growth spurt: this is called adolescent idiopathic scoliosis (AIS).[62, 63] 0.5-3% of the population is affected by AIS, no early preventive treatment is available and more than 10% of the patients require intensive brace therapy or invasive surgical correction.[3, 51, 63] While these challenges call for better understanding of the natural history of AIS, the etiology of AIS remains enigmatic.

Although the term 'idiopathic' (ίδιος=one's own and πάθος=suffering) implies that the cause of AIS is unknown and that the patient is otherwise -except for the spinal deformity- normal, many subtle abnormalities have been reported in the literature. It has been suggested that these findings could be helpful in clarifying the etiology of the disorder.[64] Even limited evidence for an abnormality in AIS patients has sometimes led to postulation of a new hypothesis on the role of the studied abnormality as unique causal factor of AIS.[2, 65] Clinicians treating patients with AIS, however, are often impressed with the absolutely normal development of the patient, both intellectually and physically, up to the moment that the spine starts to grow crooked and it is hard to understand the relevance of many of the reported more general and systemic abnormalities. In addition, evidence exists that intrinsic spinal biomechanics of the upright human spine, as well as genetics play a key role in the multifactorial causation of different pediatric spinal deformities, such as idiopathic scoliosis.[5, 66-68]

Insight in the concomitant abnormalities may assist in determining their relevance and to improve understanding of the etiological pathways of AIS. The different etiological hypotheses and genetic abnormalities have already been discussed in systematic reviews by Kouwenhoven et al., Lowe et al. and a recent review of Gorman et al., respectively.[2, 65, 66] Nevertheless, the epidemiology and relevance of the enormous number of phenotypical abnormalities in AIS patients have not been assessed to date. The purpose of this review, therefore, is to give as complete an overview as possible of all abnormalities, other than the spinal deformity or genetic factors, in AIS patients as compared to healthy adolescents. Furthermore, their relevance in furthering understanding of the etio-pathogenesis of the disease is addressed.

MATERIALS AND METHODS

Protocol

Following the PRISMA guidelines[69], we conducted a systematic review including the following subsequent steps: structured search, study selection, risk-of-bias assessment of individual studies and best-evidence-syntheses for relating risk-of-bias to consistency of effect sizes (figure 1). We did not register our review protocol.

Search strategy and study selection

Our search strategy was designed to ensure as wide a range of studies on AIS and associated abnormalities as possible. The search was conducted in PubMed and Embase digital databases in October 2013. We searched titles and abstracts using synonyms of idiopathic and scoliosis combined with Boolean operators (search syntax: "(idiopathic OR idiopathically) AND (scoliosis OR scoliotic OR scolioses OR spinal curvature)". Included

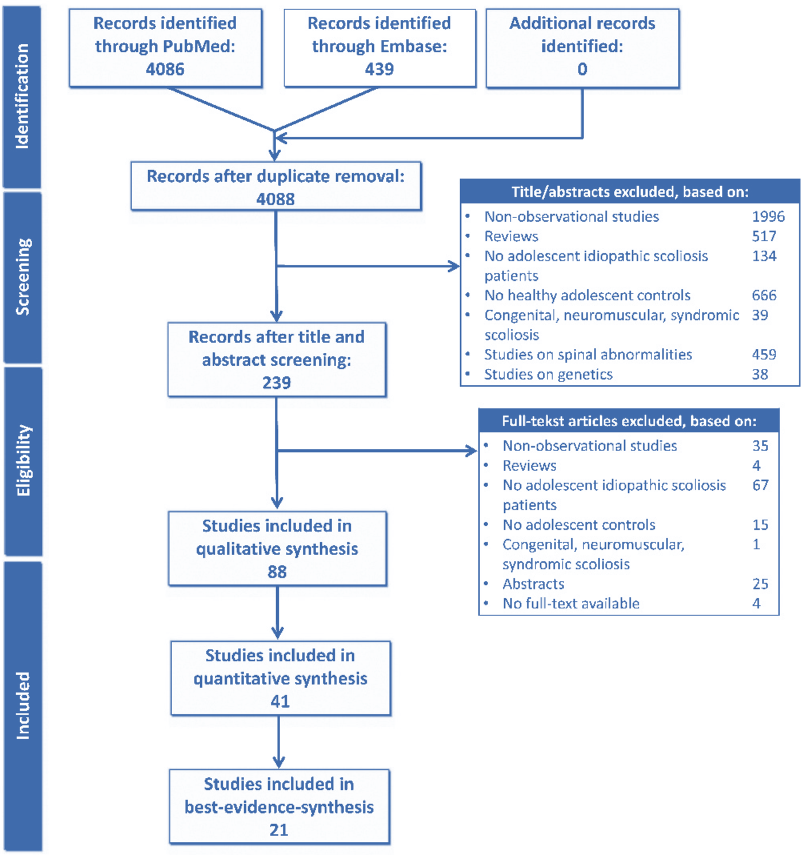

Figure 1. PRISMA flow diagram.[69]

were English, Dutch and German full-text articles and there were no publication date or status restrictions. Duplicates were removed. Abstracts were checked for relevance by two independent investigators (TS and AV) using in- and exclusion criteria that were specified in advance. The investigators reviewed full-text articles when inclusion in the review was unclear from title and abstract. Uncertainties were discussed among the investigators. All original studies that reported a potential abnormality, other than the spinal deformity or genetics, in AIS patients compared to healthy adolescents were considered for inclusion. Studies on AIS patients who underwent treatment (bracing or surgery) or with congenital, neuromuscular or syndromes associated with scoliosis were excluded. Pathologies causing neuromuscular and syndromic scoliosis were predefined; neuromuscular scoliosis: cerebral palsy, syringomyelia, Chiari type-I malformation traumatic paralysis, spinal muscle atrophy, Friedrich's ataxia, myelodysplasia, spina bifida, poliomyelitis or Duchenne's disease[70]; Syndromic scoliosis: Marfan, Turner, Rett, Prader-Willi, Angelmann, Eagle-Barrett, β-thallasemia and 22q11.2 deletion syndrome, neurofibromatosis and osteogenesis imperfecta because development of scoliosis is common in these syndromes. Reviews and case series were also excluded. Reference lists from recent reviews, related articles as indicated by PubMed and reference sections of included articles were hand-searched for additional articles.

Assessment of risk-of-bias

For the remaining studies, risk-of-bias was assessed using a six-item risk-of-bias scoring system (minimal risk-of-bias score 0, maximal risk-of-bias score 6) that was specifically developed for our research question (Table 1).[71] For any disagreement between the observers, consensus was reached by discussion. All studies were ranked according to this score and articles with a total score≥4 were included in the final analysis (low risk-of-bias: score 6; moderate risk-of-bias, score 4 or 5). We used a pre-defined cut-off value of ≤3 points (1/2 of the total score) in order to separate the high and moderate quality studies from studies with high risk-of-bias. Citations with a score ≤3 were excluded from our analysis.

Best-evidence-synthesis

Due to great heterogeneity in abnormalities and outcomes of the different studies, we conducted best-evidence-syntheses for each individual abnormality instead of a meta-analysis to quantify the relationship between each abnormality and AIS. This approach is the gold standard methodology for conducting qualitative and quantitative analyses of very heterogenic observational studies.[72] The synthesis was based on a combination of number of studies, risk-of-bias, consistency and size of the effect (figure 2). Source data (design, number of AIS subjects, number of control subjects, primary studied abnormalities, secondary differences between AIS and control cohort, mean outcome of AIS cases (μ_{AIS}), mean outcome of healthy adolescents ($\mu_{controls}$), standard deviations (σ) or errors (se)

Table 1. Risk-of-bias assessment was performed using a six-item scoring for description and validity of key information for the research question of this study and risk-of–bias.

Item	Scoring	
Selection:		
1. Is the control group representative for normal adolescents?	1	Community control
	0	HHHospital controls
	0	No description of source
2. Was other pathology excluded that possibly influences the outcome?	1	Yes
	0	No or no description
Comparability:		
3. Were the same in- and exclusion criteria (except for the spinal deformity) used for AIS and healthy adolescents?	1	Yes
	0	No or no description
Exposure/outcome:		
4. Were the observers blinded to AIS/healthy adolescent status?	1	Yes
	0	No or not documented
5. Was the data collection performed in the same standardized way for AIS cases and healthy adolescents?	1	Yes
	0	No or not documented
6. Was the primary outcome parameter for AIS cases and healthy adolescents available?	1	Available for >90% of AIS and healthy adolescents
	0	Available for <90% of AIS or healthy adolescents

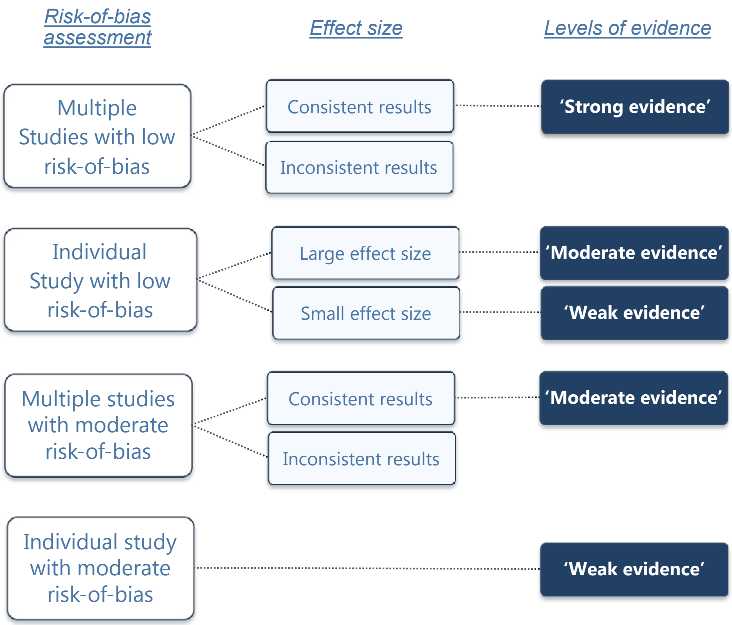

Figure 2. A best-evidence-synthesis was performed for each abnormality described in studies with satisfactory risk-of-bias.[72] Consistency was defined as ≥50% of the studies showed either a negative or positive effect of the primary outcome between AIS cases and healthy adolescents.

and significance level were reviewed and extracted into tables by one investigator and checked by the other investigator. Effect size was calculated using Cohen's *d* (Cohen's $d=(\mu_{AIS}-\mu_{controls}) / \sigma$ or $(\mu_{AIS}-\mu_{controls}) / (se\times\sqrt{n})$). A qualitative approach to data synthesis was performed to assess the level of evidence for the association of each abnormality and AIS: Consistent findings in multiple papers with low risk-of-bias were rated as strong evidence; an individual study with low risk-of-bias and large effect size (Cohen's $d>0.8$) or consistent findings in multiple studies with moderate risk-of-bias as moderate evidence; an individual study with low risk-of-bias and small effect size (Cohen's $d\leq0.8$) or with moderate risk-of-bias as weak evidence. If we were not able to calculate effect size based on poorly presented results, or conflicting findings were observed, the level-of-evidence was rated as insufficient. The literature was considered as consistent if ≥50% of the studies on different data sets showed either a negative or positive effect of the abnormality between AIS cases and healthy adolescents. For the best-evidence-synthesis, on one hand, research groups that reported on different abnormalities in multiple publications and investigated those in the same AIS dataset were considered as multiple studies. Because for most abnormalities the relation with other abnormalities is not very obvious (e.g. different vestibular organ morphometry, conus level and osteopenia), the risk of underreporting was avoided by this method. On the other hand, because of high-risk of overlap and to avoid duplicate (multiple) publication bias, multiple publications on the same abnormality studied by the same research group were counted as one study. If it was not clear whether the same dataset was used for different publications, for each abnormality only the publication with lowest risk-of-bias and largest sample size of each study group was included in the assessment of consistency of the literature. In addition, secondary outcomes were not included in the analysis to avoid duplicate (multiple) publication bias too. Risk of bias was addressed in this way, because we intended to give as complete an overview as possible of all abnormalities that have a consistent pattern of occurrence with AIS, based on the best available evidence.

RESULTS

Search, study selection and quality assessment

The PRISMA flowchart is shown in figure 1.[69] The literature search yielded a total of 4525 publications. 441 duplicate entries were identified and removed. Most initial citations (n=1996) were excluded because they did not offer any evaluation of abnormalities in untreated AIS patients, but described idiopathic scoliosis treatment outcomes. After title and abstract and full-text review, quality was assessed of eighty-eight publications. Ten (1.9%) discrepancies were found when the 528 (88 citations × six-items) scorings for risk-of-bias were compared between the independent observers (Cohen's kappa=0.962).

These were resolved by discussion. We found substantial variation in risk-of-bias of reporting among the eighty-eight studies. A further forty-seven citations were discarded because they carried high risk-of-bias. Many of them did not contain description of the selection of the AIS cohort, as well as the healthy adolescent cohort.

Hence, forty-one citations were included in the quantitative synthesis. Another major limitation of the studies was found, which was not reflected in the risk-of-bias scores of the articles. Because descriptive outcome data were not reported in a sufficient manner in the full-text articles, the effect size and direction of effect could not be calculated for twenty articles. The level of evidence of these studies on potential abnormalities in AIS was ranked as 'insufficient'. Ultimately, twenty-one publications that provided data on potential abnormalities in AIS were included in the best-evidence-synthesis.

Study demographics

The remaining twenty-one peer-reviewed publications all failed to report data from follow-up and blind assessments. All were cross-sectional observational studies and no longitudinal cohort or case-control studies were found (Table 2-4). Studies were conducted in a variety of sample sizes and subjects were enrolled in different continents. A total of 14451 AIS patients were compared with 94030 healthy adolescents. For individual studies, the number of included AIS patients and healthy adolescents varied between 10 and 11575 and between 10 and 92132, respectively. Fifteen (71%) studies recruited subjects in Asia, three (14%) in Europe and three (14%) in North-America. More specific, eleven (52%) studies were conducted by a single research group of the Chinese University of Hong Kong and four (19%) in other parts of Asia.

Potential abnormalities

In summary, fourteen potential concomitant abnormalities were studied as the primary outcome in twenty-one publications: Ten articles primarily focused on seven different neuromuscular abnormalities, four on four different anthropometric abnormalities and seven on three different metabolic abnormalities.[73-93] Two potential abnormalities were studied in multiple publications, whereas twelve were studied in one publication. The size of the effect varied between −1.13 and 1.36. Standardized risk-of-bias assessment showed that one study had the maximal risk-of-bias score of 6, and nine and eleven studies a score of 5 and 4, respectively. The common methodological limitation in the last studies with high risk-of-bias was absence or no documentation of blinding of the observers; one (5%) study described blinding of the observers for AIS/control status.[73] Three major groups of abnormalities emerged in the identified articles: neuromuscular, anthropometric and metabolic. In table 2, 3 and 4 all articles are shown, sorted per group and ranked by risk-of-bias score.

Table 2. Overview of articles identified in this study on neuromuscular concomitant abnormalities, sorted per category and ranked by risk-of-bias.

Authors	Study design	Total score	AIS n	Controls n	Primary outcome parameter	Significant differences in secondary parameters	*P*	Cohen's *d*
Neuromuscular abnormalities								
Shi et al.[73]	CS	6	20	20	Increased distance between vestibular canals	Angles between vestibular canals	0.03	−0.7
Guo et al.[74]	CS	5	57	105	Asymmetry of somatosensory evoked potentials	Decreased arm muscle strength	0.03	−0.26
Kuo et al.[75]	CS	5	22	22	Improved gait control	-	NS	−0.50
Wang et al.[76]	CS	5	50	40	Thinner cortex right cerebrum	-	0.02	−1.13
Shi et al.[77]	CS	5	50	40	Decreased volumes right and left cerebellar regions	-	0.03	−0.68
McIntire et al.[78]	CS	4	14	26	Decreased trunk muscle strength	-	<0.05	−0.71
Bruyneel et al.[79]	CS	4	10	15	Impaired gait control	-	<0.01	0.62
Yang et al.[80]	CS	4	20	20	Impaired gait control	-	NS	1.36
Sun et al.[81]	CS	4	240	120	Level of the end of the spinal cord	-	NS	0.06
Gruber et al.[82]	CS	4	36	10	Impaired gait control	-	0.03	1.66

Abbreviations: AIS=adolescent idiopathic scoliosis; CS=cross-sectional; NS= not significant X= impossible to calculate Cohen's d.

Best-evidence-syntheses

With our best-evidence-syntheses we were unable to find both strong evidence and a consistent pattern of occurrence for AIS for any of these abnormalities. Two out of fourteen potential abnormalities (gait control and bone mineral density) were described in multiple studies with moderate risk-of-bias. Despite the heterogeneity of outcome parameters in the different studies, direction of evidence and effect size were consistent and therefore, the evidence was moderate for association of these abnormalities with AIS. For nine other (neuromuscular, anthropometric or metabolic) abnormalities a consistent pattern of occurrence with AIS was found, but the evidence was weak. Moreover, three potential abnormalities were not significantly concomitant with AIS. Therefore, a total of eleven abnormalities were classified as associated with AIS with weak to moderate evidence (table 5; figure 3). In the following paragraphs, these abnormalities will be addressed.

Table 3. Overview of articles identified in this study on anthropometic concomitant abnormalities, sorted per category and ranked by risk-of-bias.

Authors	Study design	Total score	AIS n	Controls n	Primary outcome parameter	Significant differences in secondary parameters	*P*	Cohen's *d*
Anthropometric abnormalities								
Shohat et al.[83]	CS	5	11575	92132	Body height	Lower Body weight, lower body-mass-index	<0.001	0.18
Cheung et al.[84]	CS	5	621	300	Corrected body height	Lower body weight, lower bone mass, longer arm span, longer leg length, lower bone mineral density, higher bone alkaline phosphatase	0.002	0.57
Barrios et al.[85]	CS	5	52	92	Body weight	Lower body-mass-index, higher Ponderal index, lower bony weight,	<0.05	–0.41
Normelli et al.[86]	CS	4	48	28	Breast asymmetry	-	<0.05	0.99

Abbreviations: AIS=adolescent idiopathic scoliosis; CS=cross-sectional; X= impossible to calculate Cohen's d.

Neuromuscular abnormalities

Based on a large mean effect size, abnormal gait control and cortical thinning of the right cerebrum were the abnormalities most concomitant with AIS. Kuo et al., Bruyneel et al., Yang et al. and Gruber et al. compared dynamic balance control of AIS patients with normal adolescents using movable balance platforms or force plates.[75, 79, 80, 82] These four studies had moderate risk-of-bias. Overall, consistent results, a large mean effect size (1.00) and moderate evidence for an association of impaired gait control and AIS were found. In addition, the best available evidence was weak for abnormal morphometry of the vestibular organs, thinner cortex of the right cerebrum, decreased volumes of different cerebellar regions, asymmetry of somatosensory evoked potentials and decreased trunk muscle strength in AIS patients.[73, 74, 76-78] It was weak, because these abnormalities were each studied in one study. However, while the effect size of a thinner cortex of the right cerebrum between AIS patient and controls was large, it was small for the other abnormalities. In addition, weak evidence was found in a study of Sun et al. that the level of the lower end of the spinal cord (normally between T12 and L3) is <u>not</u> different between AIS cases and healthy adolescents.[81]

Table 4. Overview of articles identified in this study on metabolic concomitant abnormalities, sorted per category and ranked by risk-of-bias.

Authors	Study design	Total score	AIS n	Controls n	Primary outcome parameter	Significant differences in secondary parameters	*P*	Cohen's *d*
Metabolic abnormalities								
Lee et al.[87]	CS	5	619	300	Decreased bone mineral density	Lower body weight, increased corrected body height, lower body-mass-index, increased arm span, increased leg length, bone mineral content	<0.001	–0.94
Yu et al.[88]	CS	5	112	115	Decreased bone mineral density	Lower body-mass-index, lower body weight, right femoral neck bone mineral density	0.001	–0.45
Cheng et al.[89]	CS	4	81	220	Decreased bone mineral density	-	<0.01	–0.50
Cheng et al.[90]	CS	4	75	94	Decreased bone mineral density	Lower body-mass-index, increased arm span, increased leg length	NS	–0.19
Park et al.[91]	CS	4	19	16	Decreased bone mineral density	Decreased ability of mesenchymal stem cells for osteogenic differentiation	0.037	–0.71
Lam et al.[92]	CS	4	635	269	Impaired bone quality	Lower body weight, increased corrected body height, increased arm span, lower body-mass-index, lower bone mineral density	<0.001	–0.42
Liu et al.[93]	CS	4	95	46	Lower serum leptin level	Lower body-mass-index, longer arm span, higher level of soluble leptin receptor, lower free-leptin-index	NS	–0.24

Abbreviations: AIS=adolescent idiopathic scoliosis; CS=cross-sectional; NS= not significant.

Table 5. All identified abnormalities are presented.

Studied abnormality	Total number of studies	Highest score	Consistency results	Level of evidence*	Associated with AIS?	Mean effect size
Neuromuscular						
Impaired gait control	4 (4†)	5	Yes	Moderate	Yes	1.00
Increased distance between vestibular canals	1	6	n/a	Weak	Yes	–0.70
Thinner cortex right cerebrum	1	5	n/a	Weak	Yes	–1.13
Decreased volumes cerebellar regions	1	5	n/a	Weak	Yes	–0.68
Asymmetry of somatosensory evoked potentials	1	5	n/a	Weak	Yes	–0.26
Level of the end of the spinal cord	1	4	n/a	Weak	No	0.06
Decreased trunk muscle strength	1	4	n/a	Weak	Yes	–0.71
Anthropometric						
Increased body height	1	5	n/a	Weak	No	0.18
Increased corrected body height	1	5	n/a	Weak	Yes	0.57
Decreased body weight	1	5	n/a	Weak	Yes	–0.41
Increased breast asymmetry	1	4	n/a	Weak	Yes	0.99
Metabolic						
Decreased bone mineral density	5(2†)	5	yes	Moderate	Yes	–0.83
Lower serum leptin level	1	4	n/a	Weak	No	–0.24
Impaired bone quality	1	4	n/a	Weak	Yes	–0.42

Abbreviations: AIS=adolescent idiopathic scoliosis; n/a=not applicable.
*Level of evidence was determined using a best-evidence synthesis.
†Number of studies on different datasets

Anthropometric abnormalities

Shohat et al. showed in military records of 11575 17-year old AIS patients compared to 92132 non-scoliotic 17-year olds, the largest sample size that was found in this review, mean body heights of 163 and 162cm, respectively.[83] The effect size, however, was very limited (Cohen's *d*<0.2). From our systematic analysis, it was concluded that increased body height is <u>not</u> associated with AIS. Nonetheless, using Bjure's formula, Cheung et al. showed increased body height in 13 to 15 year old AIS patients compared to healthy 13 to 15 year olds, when trunk height was corrected for the loss due to the coronal spinal deformity.[84, 94] In addition to increased corrected body height, Barrios et al. showed

	Associated with AIS	Non-associated with AIS
Strong evidence		
Moderate evidence	**Neuromuscular** • Impaired gait control **Metabolic:** • Decreased bone mineral density	
Weak evidence	**Neuromuscular** • Different vestibular morphometry • Decreased cerebral cortical thickness • Different volumes cerebellar regions • Asymmetry of somatosensory evoked potentials • Decreased trunk muscle strength **Anthropometric** • Increased corrected body height • Decreased body weight • Increased breast asymmetry **Metabolic** • Impaired bone quality	**Neuromuscular** • End-level of the spinal cord (conus medullaris) **Anthropometric** • Body height **Metabolic** • Serum leptin levels

Insufficient evidence
Neuromuscular • Cerebellar tonsil position • Regional brain volumes • Spinal cord/vertebra length ratio • Muscle spindle function • Shoulder muscle strength • Corpus calosum volume • Electromyographic activity back muscles **Metabolic:** • Calcium intake **Other:** • Distance between aorta and vertebrae • Vital capacity

Figure 3. Level of evidence is shown for all associated and non-associated abnormalities that were identified in this systematic review. Level of evidence was determined using a best-evidence-synthesis. AIS=adolescent idiopathic scoliosis.

lower mean body weight in fifty-two AIS patients compared to ninety-two age-matched controls.[85] Further, Normelli observed significantly more left-right breast asymmetry in AIS patients compared to controls.[86] Because the last three abnormalities were studied in a single study, they were considered as associated with AIS, but the quality of the evidence was weak for all three. The relation between breast asymmetry and significantly concomitant with AIS was significant (mean effect size=0.99), while the relation of AIS with increased corrected body height and decreased body weight was smaller (mean effect sizes 0.57 and –0.47, respectively).

Metabolic abnormalities

This review included seven different publications on four metabolic abnormalities. Assessment of the quality of the data suggests that evidence for decreased bone mineral density in AIS patients was moderate, for serum leptin levels and impaired bone quality weak, and for calcium intake insufficient. Four of five articles on bone mineral density were performed by the same group from Hong Kong.[87-91] Participant of these studies were included at the same scoliosis clinic or local secondary schools and inclusion periods were not documented. Due to high risk of overlapping datasets, three of their studies were not included in the best-evidence synthesis. The effect sizes of Lee et al.

from Hong Kong (the study with lowest risk-of-bias and largest sample size) and Park et al. from Korea were used for evaluation of consistency of the identified literature on bone mineral density in AIS cases.[87, 91] Mean effect size of these two studies was large (–0.83). Therefore, decreased bone mineral density can be considered as significantly associated with AIS. In addition, impaired bone quality was also associated with AIS with a small effect size in a study of Lam et al., while serum leptin levels were not significantly associated with AIS in a study of Liu et al..[92, 93]

DISCUSSION

For better understanding of the etiology of AIS, this systematic review was designed to give as complete an overview as possible of extraspinal abnormalities that have been implicated to be concomitant with AIS. The outcome of our analysis concludes that, based on the available literature, strong evidence is lacking for a consistent pattern of occurrence of AIS and any abnormality. In addition, the abnormalities were never studied in AIS cases before the onset of the deformity. Weak to moderate evidence, however, was found for eleven abnormalities in AIS patients after the onset of the deformity. Based on a large mean effect size, four of these (impaired gait control, cortical thinning of the right cerebrum, increased breast asymmetry and decreased bone mineral density) can be considered as significantly concomitant with AIS.

After a critical review of the existing literature, a definite answer to the question that was raised in the title of this article cannot be provided. All publications on concomitant abnormalities had a cross-sectional design and the investigations were performed on AIS patients after the onset of the spinal deformity. Chronic deformation of the spine and asymmetry of the trunk can interact with many physiological systems outside the vertebral column.[62, 95] For most of the reported anomalies it remains unclear whether they occur during the development of scoliosis simultaneously with the spinal curvature and to what extent they also occur in scoliosis with a known cause, such as congenital and neuromuscular scoliosis.[96] For multiple abnormalities, including impaired gait control and decreased bone mineral density, significant correlations with Cobb angle or other severity measures has been documented, suggesting that they occur as a result rather than the cause of the deformity.[84, 87, 97] By studying populations with severe AIS curves, potential causal factors which disappeared after the spine started to grow crooked may have been missed. Thus, from an etiological perspective, the appropriateness of the cross-sectional study design of all studies that were identified is very limited. As an alternative, several researchers investigated the cause-and-effect relation of different abnormalities in animal models. For example, Machida et al. studied the onset of scoliosis in pinealectomized chickens and Lambert et al. in frogs after unilateral vestibular organ removal.[98, 99] It can be questioned, however, whether findings in animal models with iatrogenic scoliosis can be translated to humans, because natural development of idiopathic scoliosis cannot be found in any other vertebrate than man, and no invasive procedures are normally required to cause it.[9, 100, 101] Therefore, the identified data of cross-sectional studies as well as data from animal models do not clearly support the hypotheses that the described abnormalities play a role in the etio-pathogenesis of idiopathic scoliosis.

Since all neuromuscular disorders that act on the growing body by impaired gait control inevitably lead to the development of scoliosis, it has been inferred that idiopathic scoliosis is the result of a 'forme fruste' of neuromuscular disease. This has started in the 1940s with the suggestion that a latent form of poliomyelitis would play a role.[102, 103] Many patients with idiopathic scoliosis, however, function very well, often also athletically, up to the moment that they reach puberty and develop a curvature of the spine. After cessation of growth they very often do not manifest any other abnormality than their spinal deformity, and certainly no neurologic disability. In fact, it is increasingly recognized that instead of extrinsic neuromuscular factors the unique intrinsic spinal biomechanics of the upright human spine and genetic predisposing factors play a key role in multifactorial initiation of different pediatric spinal deformities, such as idiopathic scoliosis.[5, 66-68]

We searched for evidence describing any consistent abnormality, other than the deformity of the spine, in AIS patients compared to normal adolescents. Due to publication bias, it is likely that significant anomalies in AIS patients are more often reported in the literature than normal findings. In addition, most potential anomalies have been studied by an individual research group that was probably focused on one or more potential anomalies to test their own etiological hypothesis, providing high risk of confirmation bias. In this structured review we tried to minimize risk-of-bias by performing a best-evidence-synthesis. By this synthesis, we based our consideration of the directness of evidence on the appropriateness of the quality for our research question (validity), size of the effect and consistency of finding of studies with relatively lowest risk-of-bias.[72] It was observed, however, that for almost half of the identified articles (20 of 41) on this topic, descriptive statistics were poorly presented, effect size could not be calculated and that only statistical significance between AIS subjects and controls was documented. The reported statistical significance, however, is not a direct parameter for effect size, but rather a function of effect and sample size.[104] Because studies without complete descriptive data may have found significant differences with a completely irrelevant effect size, these studies were not included in the final analysis. In summary, systematic analysis of the best available data showed that several abnormalities that were initially described as associated with AIS in the literature, were classified as not associated with AIS, or as 'insufficient evidence' after the critical evaluation. Another limitation of the literature on potential abnormalities in AIS patients was that for nine associated abnormalities, only one study was found and most of these studies were performed by a single research group. It cannot be derived from our data whether multiple abnormalities were found in the same study population and have confounding relations, and whether demographic factors played a role.

The disorder that we call 'idiopathic' scoliosis is far from homogeneous, and spinal rotatory decompensation into deformity seems a rather aspecific response to a multitude of factors. From an epidemiological perspective, Rothman et al. described a model to address problems of multifactorial causation, the sufficient-component cause model. In short, "*the causal mechanism for any effect must consist of a constellation of components that act in concert*".[105] In AIS, the causal mechanisms (also known as "sufficient cause") as well as the necessary and complementary components for initiation of these mechanisms are not well understood. The diversity in components of causal pathways in AIS has complicated investigations into the multifactorial origin of idiopathic scoliosis in the past and probably will continue to do so in the future. Because of its multifactorial origin, multivariate testing is needed in studies on components of sufficient causes of AIS. Nevertheless, most studies that were identified in this review focused on a unique causal factor of AIS and used univariate analyses for this reason. Therefore, their findings may be statistical artifacts. So, to make causal inferences we should take account of the constellation of multiple components in the causal pathways of AIS, by taking account of the strength of the effect and timing of concomitant abnormalities.

CONCLUSION

Several subtle abnormalities exist in AIS patients. However, the relevance of these associated disorders for understanding the etio-pathogenesis of AIS is very limited. For now, it seems that the development of scoliosis is the growing spine's pre-conditioned response to a multitude of unknown offenses to disturb the delicate human rotational spino-pelvic balance during growth.[2, 65, 100] Understanding the relevance of the phenotypical heterogeneity of AIS patients is of great value for scientists that focus on the etio-pathogenesis of AIS.

Part I

Normal Spino-Pelvic Alignment

Chapter 3

Natural Sagittal Spino-Pelvic Alignment in Boys and Girls Before, At and After the Adolescent Growth Spurt

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Eur Spine J, 2014. In Press

ABSTRACT

Purpose. Adolescent idiopathic scoliosis occurs far more often in girls than in boys, and its initiation and progression normally takes place around the adolescent growth spurt. Despite extensive research into the topic, no solid explanation for both well-known phenomena's has been offered. The sagittal profile of the growing spine has been demonstrated previously to play an important role in the spine's rotational stiffness. Changes in this sagittal alignment around the growth spurt can be inferred to play an important role in the spine's propensity to develop a rotatory deformity, i.e. scoliosis. The aim of this study was to quantify sagittal spino-pelvic alignment and orientation in space of each individual vertebra in normal boys and girls in the beginning, at the peak and at the end of pubertal growth.

Methods. Standardized lateral radiographs of the spine of boys (n=57) and girls (n=99) between the age of seven and eighteen who underwent screening for scoliosis, but had a normal spine were enrolled in this study. Children with spino-pelvic pathology at initial screening or during follow-up were excluded. According to Dimeglio's data, subjects were classified into three groups: *before*, *at* and *after* the peak growth spurt. Seven regional sagittal spino-pelvic parameters, as well as the inclination angles of each individual vertebra between C7 and L5 compared to the gravity line, were measured semi-automatically using in-house developed software.

Results. In all subjects, the posteriorly tilted segment was longer, vertebrae T1-T8 were more posteriorly inclined and thoracic kyphosis, pelvic incidence and pelvic tilt were lower before as well as during the peak of the growth spurt, when compared to after the growth spurt ($P \leq 0.023$). Furthermore, in girls, thoracic kyphosis was smaller ($P=0.023$), the posteriorly inclined segment was longer ($P<0.001$) and T1 as well as levels T3-T11 were more posteriorly inclined ($P<0.05$) compared to boys at all stages of development. At the peak of the growth spurt, girls had more posterior inclination of upper thoracic vertebrae and lower values for thoracic kyphosis than boys ($P=0.005$).

Conclusions. These results imply that the spines of girls during the growth spurt are more posteriorly inclined, and thus rotationally less stable, compared to boys at the same stage of development, as well as compared to girls after the growth spurt. This may explain why initiation and progression of adolescent idiopathic scoliosis are more prevalent in girls around puberty.

INTRODUCTION

Some of the unexplained–but well known–characteristics of pediatric spinal deformities are that they normally develop and progress around the pubertal growth spurt, and that girls are far more often affected by adolescent idiopathic scoliosis (AIS), whereas boys are more often affected by Scheuermann's kyphosis[63, 106-108]. Although their exact etiologies have not been established, it has been recognized that certain sagittal spinal profiles are more prone to develop a spinal deformity than others[8, 30, 37, 109-112].

The sagittal configuration of the spino-pelvic complex (crucially different between humans and other vertebrates) has obvious consequences for its biomechanical loading[113], but often used parameters like thoracic kyphosis and lumbar lordosis are relatively useless for understanding biomechanical loading, since the same numerical value for kyphosis can have any different position relative to gravity. We recently showed in a biomechanical cadaver study, a human *in vivo* study as well as in a finite element model that posteriorly directed shear loads decrease the rotational stiffness of spinal

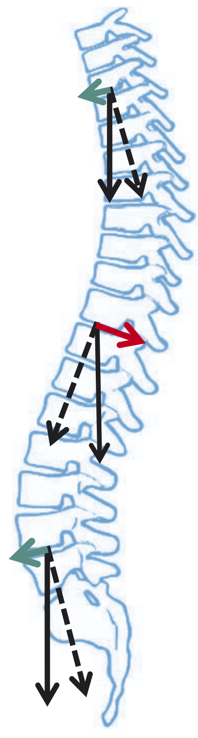

Figure 1. Schematic representation of the shear and axial components of the gravitational force that act on the upright human spine. Anteriorly (in *green*) and posteriorly (in *red*) directed shear components act respectively on anteriorly and posteriorly tilted segments of the spine.

segments[6, 26, 114]. The magnitude of these destabilizing loads, as well as the vertebrae on which they act, depends on the spatial orientation of vertebrae in the sagittal plane, since only spinal segments that are posteriorly tilted are prone to this decrease in stiffness (figure 1)[7, 23]. We recently showed that different sagittal profiles predispose to different coronal plane deformities[112]. In order to better understand spinal deformities, it is imperative to study the development of the sagittal spinal profile on the level of each individual vertebra during different stages of growth.

Sagittal spino-pelvic configuration has been studied before in normal pediatrics and young adults[7, 17, 115-120]. These studies were mainly performed in order to determine the global sagittal profile to guide how instrumented fusion of the spine should be performed at different ages. No previous study, however, has addressed the orientation of each individual vertebra as related to gravity at different ages, and these data cannot be extracted from previous studies. This specific information is essential for a better understanding of the role of the biomechanical aspects that are involved in the etio-pathogenesis of pediatric deformities. Furthermore, this information needs to be categorized per gender; and, since the timing of the growth spurt differs per gender, in relation to different phases of growth (pre-, per- and post growth spurt)[121].

To the best of our knowledge, this is the first multicenter study in which global spino-pelvic alignment as well as the spatial orientation of each individual vertebra were evaluated in normal boys and girls in relation to the beginning, the peak and the end of the pubertal growth spurt.

SUBJECTS AND METHODS

Population

Patient databases at two centers specialized in scoliosis treatment were searched for children between 7 and 18 years old that had undergone standing posterior-anterior and lateral radiological screening for scoliosis between June 2007 and June 2012. Clinical history, imaging features and radiological charts were reviewed by the investigators. Only children without spinal pathology were enrolled in this study. Most common reasons for radiological screening were referral by school nurses at annual school screening of 4-6th grade students in the state of one of our centers, referral by family physicians or concerns of parents of scoliosis patients for a deformity in their unaffected children. After ruling out spinal pathology by musculoskeletal physical examination and radiographic imaging, patients were advised to return to the clinic if they developed any symptoms of spinal pathology. The exclusion criteria were: scoliosis, other spinal, pelvic, hip or limb pathology, development of scoliosis during follow-up, syndromes associated with disorders of growth, thoracotomy, neuromuscular diseases, no standing posterior-anterior and lateral radiographs available, radiographs from other facilities or with incomplete visualization of C7-S1 and the femoral heads. For follow-up, a brief survey ("*After the screening for scoliosis in our center, was your spine diagnosed as "scoliosis" by an MD from another hospital?*") was sent to all included subjects that were mature at the time of the study (>16 years of age), to rule out scoliosis diagnosed at other facilities after the initial screening in our center.

For the initial radiological screening, similar protocols were used in both centers. Acquisition of digital, plain, full-length lateral radiographs (General Electric AL01F (General Electric, Schenectady, NY, USA); Philips Digital Diagnost (Philips B.V., Best, The Netherlands); Siemens VERTIX (Siemens, Erlangen, Germany)) was performed in an upright standing position with the hips, anterior superior iliac spines and shoulders perpendicular to the

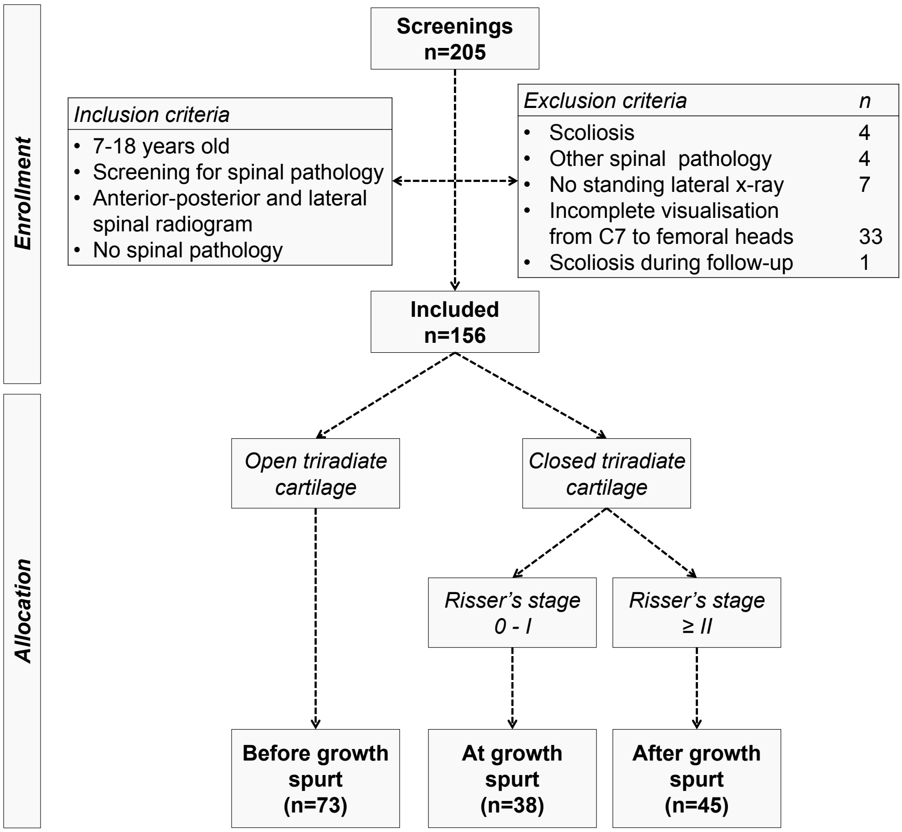

Figure 2. Subjects enrollment and cohort allocation. Pubertal status was determined according to data of Dimeglio[123, 124].

cassette and the X-ray beam aimed at T10 from the left side. With the hands on height-adjusted poles in one center and the fingertips on the zygomatic bones in the other center, subjects were standing with their arms in 45° flexion and with their hips and knees straight. They were instructed to stand in a comfortable manner and to look straight ahead.

On the posterior-anterior radiographs, one of the investigators (T.S.) determined the closure pattern of the triradiate cartilage and Risser's stage to assess skeletal maturity[122]. According to reports of Dimeglio on skeletal maturity and timing of the peak of the growth spurt, subjects were classified into three cohorts based on the closure of the triradiates as well as Risser's stage: *before*, *at* and *after* the peak of pubertal growth (figure 2)[123, 124]. These cohorts enabled the comparison of the sagittal parameters between individuals in different phases of the growth spurt, taking into account the difference in timing of the growth peak between boys and girls.

Measurement of spino-pelvic parameters

For the measurement of seven regional sagittal spino-pelvic parameters and inclination of each individual vertebra, a previously validated semi-automatic analysis method and special developed software (SpiniX, Image Sciences Institute, Utrecht, Netherlands) was used by two trained observers (figure 3)[7, 112]. They were blinded for the coronal image

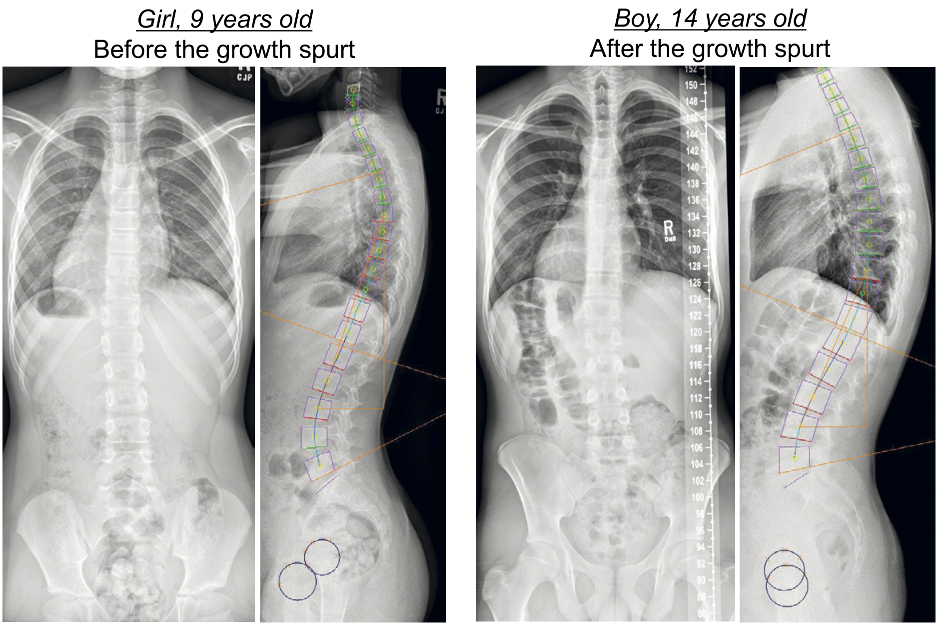

Figure 3. Anterior-posterior and lateral radiographs of two subjects showing the semi-automatic measurement of regional sagittal spino-pelvic parameters and inclination of each individual vertebra.

and cohort classification, the radiographs were analyzed semi-automatically in a random order. The investigator initiated the automatic analysis by clicking on any three points on the contours of the femoral heads, and on the four corners of each individual vertebra between C7 and S1. The software subsequently performed all computations. Thoracic kyphosis was defined as the angle between the superior endplate of T4 and the inferior endplate of T12, and lumbar lordosis as the angle between the superior endplate of L1 and the sacral endplate, respectively. Orientation and morphology of the pelvis was assessed by pelvic tilt, sacral slope and pelvic incidence[125]. In addition, the relative length of the posteriorly inclined segment of the spine, as a percentage of the total spinal length C7 to L5, and the inclination angle of the posteriorly inclined segment relative to the horizontal plane was assessed. The angle between the inferior endplate and the horizontal plane defined the exact inclination of each individual vertebra between C7 and L5. Positive values indicated anterior inclination (increased rotational stiffness) and negative values posterior inclination (decreased rotational stiffness). In a previous study on the sagittal profile of young males and females without spinal pathology, intraclass correlation coefficients and corresponding 95% confidence intervals for inter- and intraobserver variability were respectively 0.97 (0.90-0.99) and 0.96 (0.89-0.99) for measurement of the spino-pelvic parameters by this method[7].

Statistical analysis

Statistical analyses were performed in SPSS 20.0 (SPSS Inc., Chicago, IL, USA). To investigate the differences in sagittal parameters between the cohorts and between the genders, one-way analysis of variance (ANOVA) was used. Because vertebral inclination of spinal levels depends on inclination of adjacent levels, multivariate analysis of variance (MANOVA) was used to analyze the differences in vertebral inclination between the cohorts and between the genders. After homogeneity of variance was assumed by non-significant Levene's statistical tests, the level of statistical significance was extracted. For significant (M)ANOVA's, *post hoc* analyses were performed and a Bonferroni correction was applied. Pearson's correlation coefficient was used to evaluate the correlation between the sagittal spino-pelvic parameters. Results are presented as mean±standard deviation with an α level of 0.05 considered statistically significant.

RESULTS

A total of 205 initial screenings were performed during the study period in our centers. Eight patients had spinal pathology and were therefore excluded. In addition, seven subjects had no standing lateral radiograph in the digital archives and on thirty-three lateral radiographs either the femoral heads or C7-S1 were poorly visualized. Of the resulting subjects, seventy-two were full-grown (mean age 17.0±1.7 years, skeletal parameters indicating cessation of growth) at the time of the current study, forty of these (i.e. 57%) returned the follow-up questionnaire. By this questionnaire, one subject was excluded for diagnosis of scoliosis in another hospital after the initial screening. No evidence for spinal or pelvic pathology was found for the resulting subjects in the clinical and radiological charts. The 156 remaining subjects were on average 12.0±2.3 years old and ninety-nine (63%) were girls. After the determination of the stage of skeletal maturity, seventy-three (47%) subjects were before the peak of the growth spurt, thirty-eight (24%) at the peak of the growth spurt and forty-five (29%) were skeletally mature. Detailed demographics per cohort are shown in table 1.

Thoracic kyphosis, pelvic tilt and pelvic incidence were significantly increased at the end of pubertal growth as compared to both earlier phases of development ($P<0.001$, $P=0.004$ and $P=0.020$, respectively; Table 2). Lumbar lordosis and sacral slope were not

Table 1. Demographics.

	Before growth spurt (n=73)	**At growth spurt (n=38)**	**After growth spurt (n=45)**
Girls	44 (60%)	31 (82%)	24 (53%)
Mean age girls ±SD in years (range)	9,9±1,4 (7,0-12,5)	12,3±1,1 (10,6-15,7)	14,0±1,4 (11,4-16,7)
Mean age boys ±SD in years (range)	10,6±1,9 (7,1-14,5)	13,7±0,7 (12,7-14,7)	14,8±1,4 (13,1-17,4)
Triradiate cartilage closed	0 (0%)	38 (100%)	45 (100%)
Risser's stage	0: 72 (100%)	0: 22 (58%) I: 16 (42%)	II: 18 (40%) III: 8 (18%) IV: 10 (22%) V: 9 (20%)

Table 2. Average values for spino-pelvic parameters in the different age cohorts with standard deviations.

Parameter	**Before growth spurt (n=73)**	**At growth spurt (n=38)**	**After growth spurt (n=45)**	***P***
Thoracic kyphosis (°)	29±8	34±10	39±9	<0.001*
Lumbar lordosis (°)	53±10	57±13	56±10	>0.05
Sacral slope (°)	38±7	40±9	39±9	>0.05
Pelvic tilt (°)	3±8	5±9	9±8	0.004*
Pelvic incidence (°)	41±10	44±14	47±12	0.020*
Declive segment length (%)	76±9	71±11	64±11	<0.001*
Declive segment inclination (°)	15±6	16±5	17±5	>0.05

*$P<0.05$

Table 3. Average values for spino-pelvic parameters in boys *versus* girls with standard deviations.

Parameter	Boys (n=57)	Girls (n=99)	*P*
Thoracic kyphosis (°)	34±9	32±10	0.023*
Lumbar lordosis (°)	54±10	55±11	>0.05
Sacral slope (°)	39±9	38±8	>0.05
Pelvic tilt (°)	7±8	4±9	>0.05
Pelvic incidence (°)	45±11	43±12	>0.05
Declive segment length (%)	67±11	74±11	<0.001*
Declive segment inclination (°)	15±6	16±5	>0.05

*$P<0.05$

different between the cohorts. The relative length of the potentially unstable posteriorly inclined segment decreased during skeletal development, from 76±9% to 71±11% to 64±11% respectively for each developmental cohort ($P<0.001$). The inclination angle of the posteriorly inclined segment relative to the horizontal plane – as measured over only the posteriorly inclined vertebrae - was not significantly different between the cohorts.

Differences between genders were also significant. Thoracic kyphosis, as well as total length of the posteriorly inclined segment differed significantly between the genders in all growth cohorts (table 3). In boys, mean thoracic kyphosis was 34±9° and the percentage of the spine that was posteriorly inclined was 67±11%. On the contrary, the thoracic kyphosis in girls was lower (32±10°; $P=0.023$) and the posteriorly inclined segment longer (74±11%; $P=0.001$). In more detail, it was observed that the difference in thoracic kyphosis between the genders depended on developmental status: While thoracic kyphosis was similar between boys and girls before and after the peak of the growth spurt, it was significantly different at the peak of the growth spurt ($P=0.005$; figure 4). Girls had a significantly lower value for thoracic kyphosis than boys, due to the differences in age at which the growth spurt commences. Furthermore, the posteriorly inclined (rotationally less stable) segment of girls was longer at all stages of development. ($P<0.001$).

Analyses of vertebral inclination of each individual vertebra in boys and girls together led to the findings that posterior inclination of T1-T8 was significantly greater and posterior inclination of T12-L2 significantly lower before and at the peak of the growth spurt as compared to after the peak of adolescent growth ($P<0.05$). Compared between genders, spinal levels T1 and T3-T9 of girls were significantly more posteriorly inclined than in boys at all stages ($P=0.012$; figure 5). Vertebral inclination of T10, T11 and L3-L5 did not significantly differ between the cohorts or the genders.

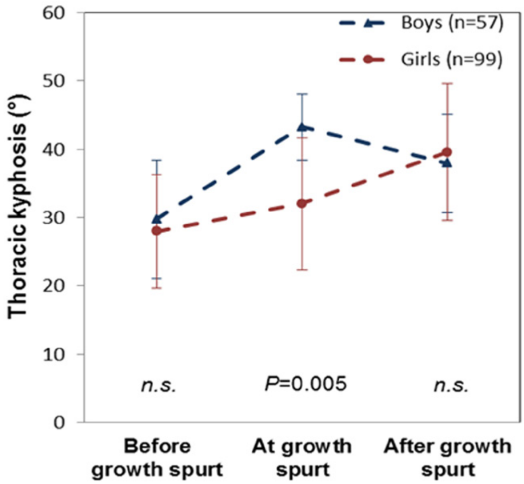

Figure 4. Differences in thoracic kyphosis between boys and girls during adolescent growth. Error bars indicate standard deviations and significance level is shown for the differences between boys and girls within the cohorts. n.s. = not significant.

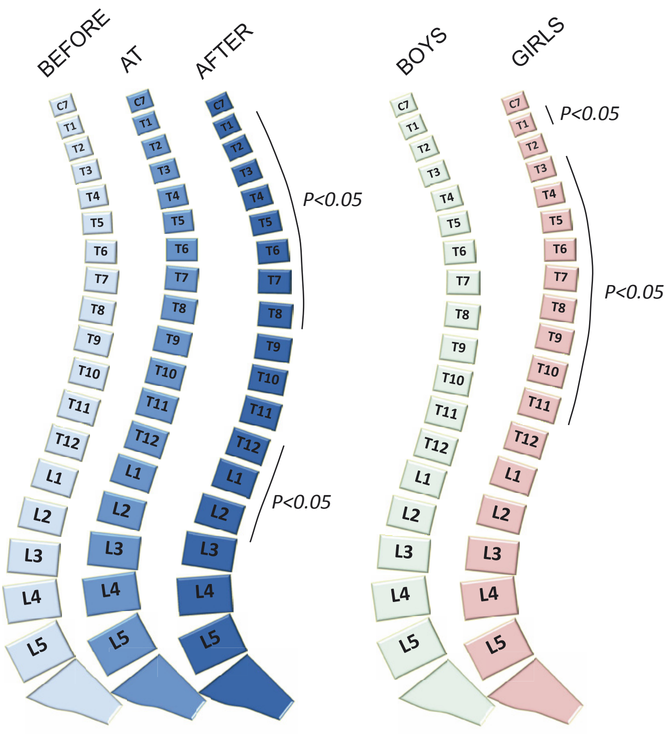

Figure 5. Illustrations of the differences in vertebral inclination between the cohorts and between the genders.

Interestingly, similar to the thoracic kyphosis, the differences in posterior inclination of the vertebrae between boys and girls depended on growth status (figure 6) as indicated by a significant interaction effect between gender and growth cohort in the multivariate analysis of variance (P=0.027). The spatial orientation of vertebrae in girls was not significantly different before and at the peak of the adolescent growth spurt (P>0.05). However, from peak of pubertal growth to thereafter, T1-T8 became less posteriorly inclined (P≤0.048). In boys, posterior inclination of the same vertebral levels also decreased during the growth spurt. In contrast to girls, the decrease in posterior inclination of vertebrae was observed at an earlier stage as far as developmental status is concerned, between the beginning and the peak of adolescent growth (P≤0.04) while no differences were found between later stages of the growth spurt (P>0.05).

Significant correlations between the spino-pelvic parameters were observed (figure 7). Interestingly, the length of the posteriorly inclined segment correlated negatively with the thoracic kyphosis, as well as with the pelvic incidence and pelvic tilt. In other words, a smaller pelvic incidence implies a longer posteriorly inclined segment. There was no correlation of the length of the posteriorly inclined segment with the pelvic incidence.

DISCUSSION

The role of upright biomechanics of the spine in the aetio-pathogenesis and evolution of spinal deformities has been conclusively demonstrated[5, 30, 112, 120, 126, 127]. In order to better understand why girls around peak height velocity are more prone to the development of progressive idiopathic scoliosis than boys, sagittal spino-pelvic configuration was evaluated both globally and per vertebra, in normal boys and girls in the beginning, at the peak and after the adolescent growth spurt. We found that before and at the peak of the growth spurt, children had relative lower pelvic incidence and pelvic tilt, smaller thoracic kyphosis and more posterior inclination of individual vertebrae as compared to after the peak of the growth spurt. In addition, we found that girls had smaller thoracic kyphosis compared to boys, and individual upper thoracic vertebrae were more posteriorly inclined, especially around peak growth velocity. In the literature, a relatively wide variation in sagittal alignment and pelvic orientation and morphology was observed with spinal configuration depending on age, gender and race[7, 115, 128]. It has been repeatedly reported that during physiological growth thoracic kyphosis and pelvic incidence increase slightly, leading to the development of the adult configuration at the end of growth[17, 116-120]. Our study confirms that the delicate balance of the upright human spine is definitely different between boys and girls and between different phases of pubertal growth.

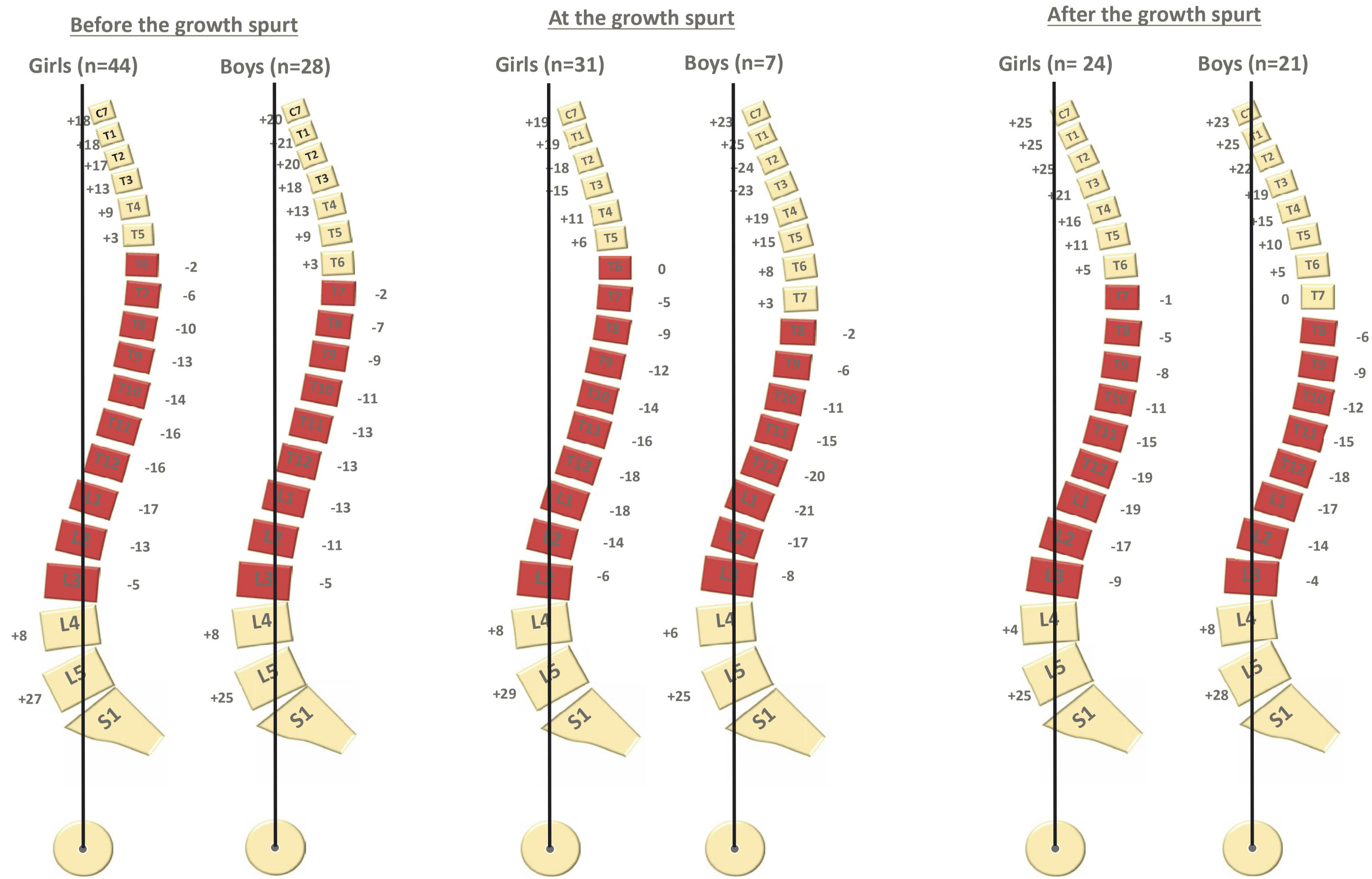

Figure 6. Exact vertebral inclination in the sagittal plane in boys and girls in the different cohorts. Posteriorly inclined vertebral levels are illustrated in *red*.

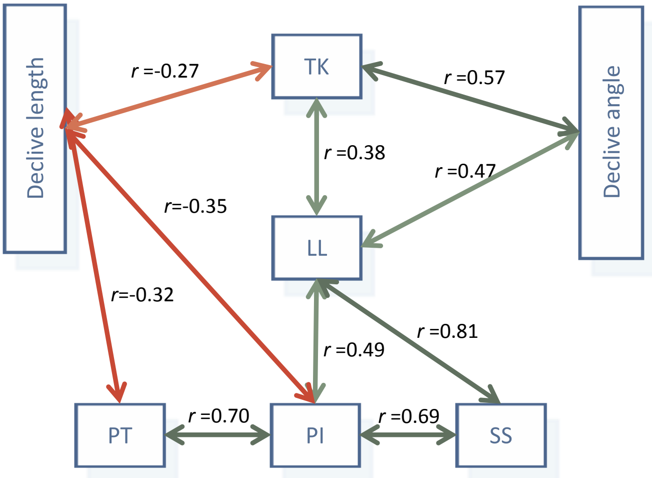

Figure 7. Significant correlations between the different sagittal parameters of the spine, pelvis and posteriorly inclined segment are shown. Potential correlations that were not statistically significant ($P>0.05$) are not included in the figure. r=Pearson's correlation coefficient, TK=thoracic kyphosis, LL=lumbar lordosis, PT=pelvic tilt, PI=pelvic incidence, SS=sacral slope.

There has been increased recognition of the importance of the sagittal alignment of the spine in relation to its normal functioning and in the etio-pathogenesis of pediatric spinal deformities[8, 30, 37, 109-112]. Although in humans as well as in all other vertebrates, predominant loading of the spine is in an axial direction, the exact sagittal alignment of the double-S shaped human spine in relation to the pelvis determines whether individual vertebrae are, in addition to this axial loading, subject to either an anteriorly directed, or a posteriorly directed vector (figure 1)[113]. In a previous study, we have shown that an excess of posterior shear leads to a decrease in rotational stiffness of the involved segments[6]. Therefore, the more the spine exhibits areas with posteriorly tilted vertebrae, the more these segments are prone to develop a rotational deformity (i.e. scoliosis).

Observation of reduced kyphosis in pre- and pubertal girls has been observed previously by Willner, Dickson and Poussa[30, 120, 126, 127]. These studies, however, did not take the position of the kyphosis, nor of the individual vertebrae relative to the gravity line into consideration. Mac-Tiong et al. already reported a tendency for posterior tilt of the thoracic and lumbar spine in pediatrics as compared to adults[17]. It is well known that 84-89% of scoliosis develop without a known cause in previously healthy children during the adolescent growth spurt, and that progression occurs 5.4 times more in girls than in boys[35]. Our results demonstrate the differences in posterior inclination of the spine in different phases of the growth spurt. Most posterior inclination was found in girls around the peak of the adolescent growth spurt. Therefore, the sagittal alignment of the spine of pubertal girls apparently predisposes them to the initiation or progression of AIS.

Although thoracic lordosis has been incriminated as an initiating factor in scoliosis (Dickson, Roaf, Sommerville[30, 34, 35, 37]), we believe that not the thoracic lordosis in itself, but rather the spatial orientation of individual vertebrae, and subsequently the amount of posteriorly directed shear loads contribute to the rotational instability, leading to rotation, lateral deviation and lordosis[5, 8]. According to this concept, it can be inferred that the area of the spine in which a rotational deformity has a chance to develop, is based on the posterior inclination of the spine and magnitude of posteriorly directed shear loads before the onset of the deformity.

Despite the fact that variation in timing of the growth spurt was not taken into account in previous radiographic studies, evidence was found for differences in the sagittal spinal profile and pelvic morphology between children of different ages, as well as between boys and girls in other studies as well[7, 17, 115-120]. In children between 3 and 15 years old, Cil et al. revealed that thoracic kyphosis and lumbar lordosis increase during growth and that the thoracic apex is localized lower in late adolescence as compared to younger ages[118]. Moreover, they observed that development of the lumbar lordosis starts before puberty and that thoracic kyphosis starts to develop later.

In 2013, Clément et al. did not observe a direct relation between thoracic kyphosis and sagittal pelvic parameters in patients with AIS[129]. Similarly, in our evaluation on sagittal spino-pelvic alignment of non-scoliotic spines there was no significant correlation between pelvic parameters and thoracic kyphosis. Indirectly, however, it was observed that lumbar lordosis as well as the length of the posteriorly inclined segment correlated significantly with the pelvic incidence and pelvic tilt, as well as with thoracic kyphosis. The impact of ontogenetic changes in sagittal pelvic morphology on sagittal alignment of the thoracic spine can however not be derived from this study.

Thoracic kyphosis has been defined differently in the literature. Instead of measurement of the angle between the most tilted kyphotic segments, which can vary significantly, we preferred to measure thoracic kyphosis between predefined segments (T4-T12) for better comparability between the cohorts, in line with Korovessis et al., Kobayashi et al. and Janssen et al.[7, 23, 109, 130]. In contrast to earlier studies, our study provides an assessment of the direction of vertebral loading by including the exact inclination of individual vertebra in the analysis.

Comparing sagittal spinal alignment of adolescent boys and girls, Cil et al. reported significant differences without further specification and Mac-Thiong et al. reported that the inclination of the thoracic spine is different between boys and girls[17, 117, 118, 131]. Unfortunately, despite the fact that boys and girls of the same chronologic age are normally not in the same stage of skeletal development (girls enter their period of rapid pubertal growth on average two years earlier than boys), gender was not taken into consideration in their final analyses[121]. In our radiographic study, we classified the children not according to chronological age, but in relation to the phase of the growth spurt according to data provided by Dimeglio[123, 124]. We found that peak growth velocity occurred on average 1.4 years earlier in the girls as compared to the boys. This has very important biomechanical consequences, since at this time, the spine is still more posteriorly inclined, implying less rotational stiffness and more propensity to develop scoliosis[5, 26, 114]. Recently, similar observations were done by Dolphens et al. in a study on digital images and direct body measurements of 1196 Flemish school-children[132-134].

CONCLUSIONS

Our results imply ontogenetic variation in the sagittal spinal configuration of boys and girls. Girls are going through their period of most rapid growth at a time when the whole spine is still more posteriorly inclined, whereas the boys have developed more thoracic kyphosis with much less posterior inclination before peak height velocity[30, 120, 126]. Therefore, the spines of girls before and at the peak of the growth spurt are more posteriorly inclined and affected by greater posteriorly directed shear loads than in boys at the same stage of skeletal development, rendering them less rotationally stable. This, in line with earlier biomechanical experiments, seems to offer an explanation why the female spine during the pubertal growth spurt is less protected against the development of a rotational deformity like scoliosis.

Chapter 4

Evolution of the Ischio-Iliac Lordosis during Natural Growth and Its Relation With the Pelvic Incidence

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ABSTRACT

Purpose. Human fully upright ambulation, with fully extended hips and knees, and the body's center of gravity directly above the hips, is unique in nature, and distinguishes humans from all other mammalians. This bipedalism is made possible by the development of a lordosis between the ischium and ilium; it allows to ambulate in this unique bipedal manner, without sacrificing forceful extension of the legs. This configuration in space introduces unique biomechanical forces with relevance for a number of spinal conditions. The aim of this study was to quantify the development of this lordosis between ischium and ilium in the normal growing and adult spine and to evaluate its correlation with the well-known clinical parameter, pelvic incidence.

Methods. Consecutive series of three-dimensional computed tomography scans of the abdomen of 189 children and 310 adults without spino-pelvic pathologies were used. Scan indications were trauma screening or acute abdominal pathology. Using previously validated image processing techniques, femoral heads, center of the sacral endplate and the axes of the ischial bones were semi-automatically identified. A true sagittal view of the pelvis was automatically reconstructed, on which ischio-iliac angulation and pelvic incidence were calculated. The ischio-iliac angle was defined as the angle between the axes of the ischial bones and the line from the midpoint of the sacral endplate to the center of the femoral heads.

Results. A wide natural variation of the ischio-iliac angle (3-46°) and pelvic incidence (14-77°) was observed. Pearson's analysis demonstrated a significant correlation between the ischio-iliac angle and pelvic incidence (r=0.558, P<0.001). Linear regression analysis revealed that ischio-iliac angle, as well as pelvic incidence, increases during childhood (+7° and +10°, respectively) and becomes constant after adolescence.

Conclusions. The development of the ischio-iliac lordosis is unique in nature, is in harmonious continuity with the highly individual lumbar lordosis and defines the way the human spine is biomechanically loaded. The practical parameter that reflects this is the pelvic incidence, both values increase during growth and remain stable in adulthood.

INTRODUCTION

In 1950, anthropologist Washburn pointed out the role of morphological changes of the pelvis as a crucial step forward towards pertinent bipedalism in human evolution.[10] Human bipedalism is unique, because it is characterized by an orthograde, double S-shaped spine, pendular limb motion and simultaneous extension of the hips and knees. This provided the evolutionary advantage that the hands could be used for non-locomotive tasks.[13, 135, 136] Already in early hominid specimens, it was found that lordotic angulation of the ilium relative to the ischium, combined with the shortening of the ilium, enabled the delicately balanced upright position of the human spine. The weight of the upper body was carried straight above the pelvis, while the potential for femoral extension was preserved by the unchanged orientation of the ischium.[13, 60, 135, 136] Even in human's closest relatives (chimpanzees and bonobo's) there is almost no lordotic

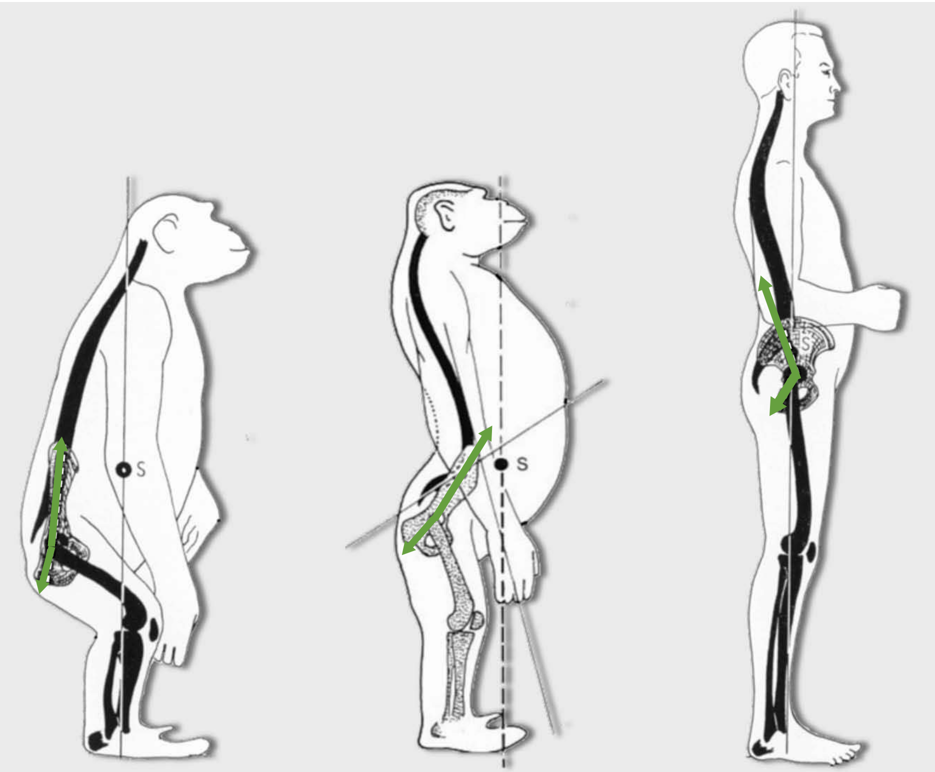


Figure 1. Like all vertebrates, human primates typically display a 'bent-hip, bent-knee' posture during quadrupedal locomotion but also during bipedal locomotion to preserve the potential of hip extension by the ischiofemoral muscles (*left*). Occasionally they could adopt a man-like fully erect posture with fully extended knees, but that would require an extreme lordosis of the lumbar spine (*middle*). Due to a lordotic angulation of the ischium and ilium, only humans are able to stand upright with only a relatively small lumbar lordosis in order to position the center of body mass (S) directly above the pelvis (*right*).

angulation between the ischium and ilium.[136-138] When a primate tries to stand upright, the trunk simply swings up on the femoral heads, to a point that the ischium points almost directly downward. The ischium, however, is the lever arm for the ischio-femoral muscles and plays an important role in the extension of the hips, and thus in forceful ambulation. In upright position with the ischium pointing straight down, the extensors of human primates will run out of power by the time the femoral shaft is vertical (Figure 1). For occasional bipedal locomotion, primates need a typical 'bent-hip, bent-knee' posture that results in the trunk being anterior to the femoral heads, or an extreme lumbar lordosis in order to position the center of mass of the upper body straight above the supporting legs.[137-139] For an energy-efficient human bipedal locomotion, however, lordotic angulation of the ilium relative to the ischium was a prerequisite to be able to walk upright, while the potential of forceful femoral extension was preserved.[60, 139, 140] As a consequence of the lordotic ilio-ischial angulation and shortening of the ilium, the sacroiliac angulation had to increase as well in order to maintain the diameter of the bony birth canal.[10, 11]

The fact that this unique human posture and ambulation simultaneously introduces unique biomechanical loading of the human spine, with unique consequences for spinal pathology, has received relatively little attention in the literature.[5] In the field of spinal pathology, there is increasing recognition of the importance of the morphology of the pelvis as a determinant of pelvic orientation and a regulator of global sagittal spinal alignment.[17, 18, 117, 141-144] In clinical practice, pelvic morphology and orientation are usually assessed on lateral radiographs, using the pelvic incidence, pelvic tilt and sacral slope, respectively.[20, 143] More specific, pelvic incidence describes the fixed position of the sacral endplate relative to the femoral heads, whereas pelvic tilt and sacral slope describe the variable position of the pelvis in space. Using the pelvic incidence, several investigators have shown that pelvic morphology, as well as global spinal parameters, changes during normal growth.[17, 117, 118, 120] Furthermore, sagittal spinal alignment has been demonstrated to play an important role in the initiation and progression of certain spinal deformities that are acquired during growth, such as idiopathic scoliosis, spondylolisthesis and Scheurmann's disease.[1, 5, 30, 31, 145, 146] The prerequisite for this uniquely human sagittal alignment, namely the lordotic angulation between the ischium and ilium, has so far received little attention and has never been quantified.[15] The aim of this study is therefore to quantify this lordotic angulation between the ischium and ilium in the normal growing and adult spine, and to evaluate its correlation with the pelvic incidence as a well-known parameter of sagittal balance.

MATERIALS AND METHODS

Population

After approval by our institutional ethics committee, our existing database of computed tomography (CT) images was searched to define two cohorts of patients, pediatrics (0-17 years of age) and adults (18 years of age or older). All patients had undergone CT examination for reasons unrelated to spinal pathology. Both cohorts consisted of all patients that had undergone CT examination of the abdomen for acute abdominal pathology or trauma screening at the emergency department of our institution (University Medical Center Utrecht, The Netherlands) between June 2005 and December 2012. Clinical and radiographic medical charts were reviewed by two orthopaedic surgery residents to rule out pre-existent spinal pathology. Patients with clinical or radiological evidence for trauma of the spine or pelvis, any pathology or previous surgery of the pelvis, spine or hips, or syndromes associated with disorders of growth were excluded. CT scans without complete visualization of the pelvis, including the most distal parts of both ischia, femoral heads and L5, or severe artifacts also led to exclusion. The scans were acquired with Philips Brilliance 16 and 64 scanners (Philips Medical Systems Nederland B.V., Best,

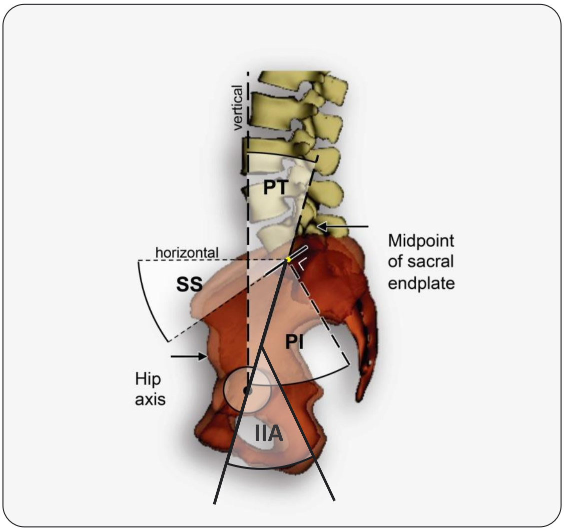


Figure 2. Typically, pelvic morphology and orientation in the sagittal plane are described by three parameters: the sacral slope (SS), pelvic tilt (PT), and pelvic incidence (PI). The SS represents the angle between the sacral endplate and the horizontal line, the PT is defined as the angle between the vertical and the line connecting the midpoint of the sacral endplate to the hip axis, and the pelvic incidence is defined as the angle between the perpendicular of the sacral endplate and the line connecting the midpoint of the sacral endplate to the hip axis. Ischio-iliac angle (IIA) is represented by the angle between the ischium and ilium, and was defined as the mean angle between the axis of the left and right ischium, and the same line connecting the midpoint of the sacral endplate to the hip axis.

The Netherlands), and consisted of axially reconstructed images with 0.4-1.0 mm pixel size and 3.0-4.0 mm slice thickness. For each subject, age and gender were documented and used for subgroup analyses.

Measurement of pelvic parameters

Special in-house developed software was used to measure the pelvic incidence and ischio-iliac angle semi-automatically, in a systematic and reproducible way. The software was previously validated for pelvic incidence measurement on three-dimensional (3-D) CT scans.[147] The computerized method (see supplementary material) was initiated by three click points that were manually indicated by one of the investigators, one within the corpus of L5 and one within each femoral head. From these points, the different anatomical structures of the pelvis were localized automatically in 3-D (Figure 3): The midpoint of the sacral endplate was found by localizing the endplate below the L5 ver-

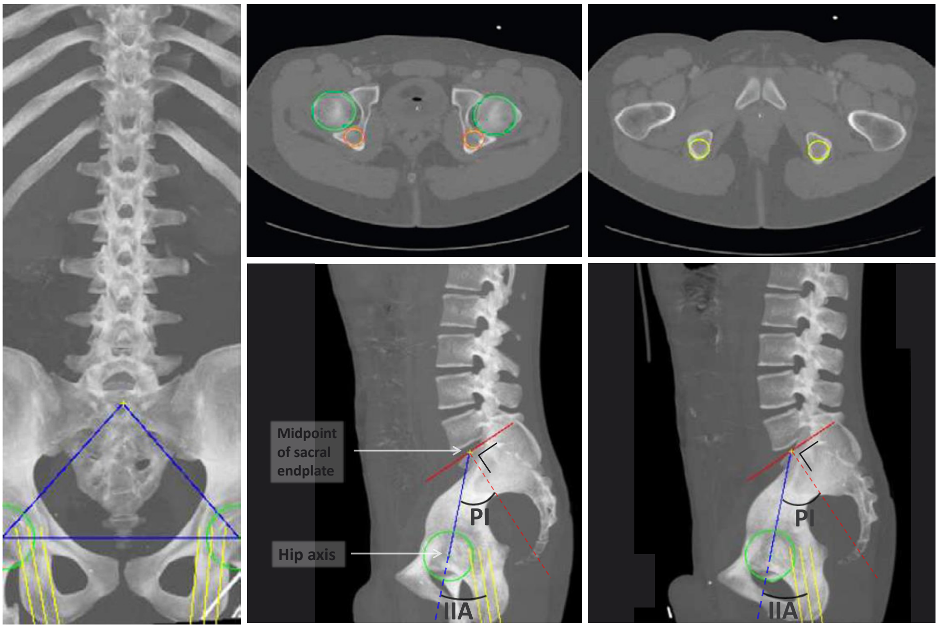


Figure 3. Computerized measurement of the ischio-iliac angle (IIA) and pelvic incidence (PI) on a computed tomography scan of the abdomen in a 16-year-old male, using in-house developed software. Different projections are shown: (*left*) multiplanar reformatted image in the coronal plane, (*top middle*) transverse plane at the hip axis, (*top right*) transverse plane 5 cm caudal of the hip axis, (*bottom middle and right*) multiplanar reformatted images in the perfect sagittal view (exactly in line with the hip axis) showing the maximal intensity projection of the left and right half of the pelvis. The *green* circles indicate the spheres that best fit to the edges of the femoral heads in three dimensions (3-D), with their centers representing the hip axis. The *yellow* circles and lines indicate the cylinders that best fit to the edges of the ischia in 3-D, with their axis representing the axis of the ischium. The *blue* triangle connects the centers of the two femoral heads (hip axis) and the midpoint of the sacral endplate. The *red* line represents the inclination of the sacral endplate.

tebral body and by the midpoint of the lines between the anterior and posterior edge, and between the left and right edge of the endplate. The centers of the femoral heads were localized by the exact centers of the spheres that best fit automatically between the 3-D edges of the femoral heads. The midpoint between the center of the left and right femoral head represented the midpoint of the hip-axis. The centers of the femoral heads and sacral endplate served to determine the location of both ischia. The orientation of the axes of both ischia were automatically determined from a cylinder that best fit to the edges of each ischium, mimicking the orientation from ischial tuberosity, ischial body and inferior-posterior part of the acetabulum. Based on the orientation of the femoral heads, multiplanar 3-D image reformation was performed to obtain a 'true' sagittal view of the pelvis in which the centers of the femoral heads were exactly in line. On this oblique image, the ischio-iliac angle and pelvic incidence were calculated automatically. *Pelvic incidence* was defined as the angle between the line perpendicular to the sacral plate at its midpoint and the line connecting this point to the hips-axis, as described by Legaye et al..[125] We defined the *ischio-iliac angle* as the angle between the axes of the ischia as determined by computer calculation, and the line connecting the midpoint of the sacral endplate to the hip axis (Figure 2).

Measurement validation

Measurement of pelvic incidence on 3-D CT images was validated in a previous study: high consistency between manual and computerized pelvic incidence measurements (intraclass correlation coefficient, ICC=0.961) and high interobserver reliability (ICC=0.994) was found.[147] Validation of the ischio-iliac angle measurement method was performed by three observers on a subgroup of 14 randomly selected CT scans of subjects with different ages and gender. Differences between manual and computerized measurements, as well as between different observers were evaluated. For the manual measurement, the observers determined (1) the inclination and midpoint of the sacral plate, (2) the centers of both femoral heads and (3) both ischia on 3-D images. For the computerized measurement, the observers initiated the automatic calculation by manually placing three click points within each femoral head and the L5 vertebral body. In both the manual and automatic measurement method, the ischio-iliac angle was calculated on the image on which the femoral heads were in line with a 'true' sagittal view. The mean absolute difference (MAD) and ICC assessed the variability between the computerized and manual method, and between the observers.

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were computed, providing the mean, standard deviation (SD) and range. Before testing, normality of distribution was verified using Q-Q plots and

Kolmogorov-Smirnov tests. Potential outliers were identified, original data checked and the effect of legitimate outliers on t-tests was evaluated. Pearson's correlation analysis determined the correlation coefficient (r) between the pelvic incidence and ischio-iliac angle, ischio-iliac angle and age, and pelvic incidence and age in pediatrics and adults. Correlations <0.50 were defined as 'moderate', between 0.5 and 0.75 as 'good', and >0.75 as 'excellent'. Linear regression analysis was used to determine the changes of pelvic parameters with age. For comparison of continuous parameters between groups (pediatrics *versus* adults, and males *versus* females), Levene's test was used to test the equality of variances, and independent samples t-test was used to test for statistical differences. The statistical significance level was set at 0.05.

RESULTS

Out of 1728 CT scans, 499 scans (189 pediatrics and 310 adults) were included in this study. The main reason for exclusion of pediatric patients was incompleteness of the scan, whereas for adults it was the suspicion of minor spinal trauma. The mean age of the pediatric cohort was 10.8±5.6 years (range, 0.0-17.9), 65 (34%) were girls. Q-Q plots showed that relatively more adolescents (10-17 years of age) than infants and juveniles (0-9 years of age) could be included. However, when the pediatric age group was categorized into nine two-year age cohorts, at least 12 children could be enrolled in each cohort, and the number of included pediatric patients per cohort was evenly distributed. The mean age of the adult cohort was 44.5±17.6 years (range, 18.0-87.0) and 149 (48%) were females. In the adult cohort, the subjects were evenly distributed among ten-year age cohorts.

A wide variation in the ischio-iliac angle and pelvic incidence was observed within the study population, both parameters were normally distributed in the pediatric and adult cohort, and no significant outliers were identified. The mean ischio-iliac angle was 23±8° (range, 3-46°) and the mean pelvic incidence was 45±11° (range, 14-77°; figure 4). A statistically significant correlation and linear relation was observed between the ischio-iliac angle and pelvic incidence (r=0.56, P<0.001, ischio-iliac angle = 0.4 × pelvic incidence + 6.3). Both parameters differed significantly between the pediatric and adult cohort (P<0.001) (Table 1). Correlation analysis revealed significant, but moderate correlation between the ischio-iliac angle and age in the pediatric cohort (r=0.29, P<0.001), and no statistical significant correlation in the adult cohort. Linear regression analysis showed that the ischio-iliac angle increased by 0.4° per year during childhood (ischio-iliac angle = 0.4° × age + 15), from 15° to 22°, and became constant during adulthood (figure 5). The pelvic incidence correlated moderately with age in both pediatric (r=0.32, P<0.001)

Table 1. Mean ischio-iliac angle and pelvic incidence with standard deviation (SD), range and level of statistical significance (*P*) for the pediatric and adult cohort, and for the complete study population.

	Study population (n=499)		**Paediatrics (n=189)**		**Adults (n=310)**		
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	***P***
Ischio-iliac angle (°)	23 (8)	3-46	19 (7)	3-40	26 (7)	9-46	<0.001
Pelvic incidence (°)	45 (11)	14-77	39 (10)	14-74	48 (11)	20-77	<0.001

Table 2. Mean ischio-iliac angle and pelvic incidence with standard deviation (SD), range and level of statistical significance for boys and girls in the pediatric cohort, and for males and females in the adult cohort.

	Boys (n=124)		**Girls (n=65)**		
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	***P***
Ischio-iliac angle (°)	18 (7)	3-35	20 (7)	4-40	n.s.
Pelvic incidence (°)	38 (10)	14-71	40 (10)	17-74	n.s.
	Males (n=161)		**Females (n=149)**		
	Mean (SD)	Range	Mean (SD)	Range	*P*
Ischio-iliac angle (°)	25 (7)	9-42	26 (6)	12-46	n.s.
Pelvic incidence (°)	48 (10)	25-77	48 (11)	20-75	n.s.

n.s. = not significant

and adult (r=0.21, P<0.001) cohorts. More specifically, regression analysis showed that the pelvic incidence increased for 0.6° per year, from 33° to 44°, during growth (pelvic incidence = 0.6° × age + 33), and increased for 0.1° per year during adulthood (pelvic incidence = 0.1° × age + 42). Taking into account the effect of age, no statistical differences between both pelvic parameters were observed between the genders in the pediatric or adult cohort (Table 2).

Reliability and validity of the measurements

The comparison of manual and computerized measurements of the ischio-iliac angle revealed MAD of 3.6° (ICC=0.857). In addition, interobserver reliability analysis for the manual and automatic ischio-iliac angle measurement methods showed high reliability (MAD=1.0° and ICC=0.993 for manual, and MAD=0.2° and ICC=0.999 for automatic method).

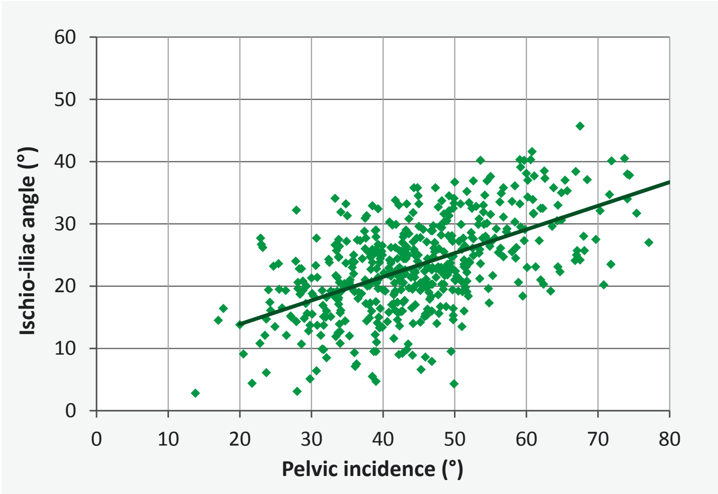
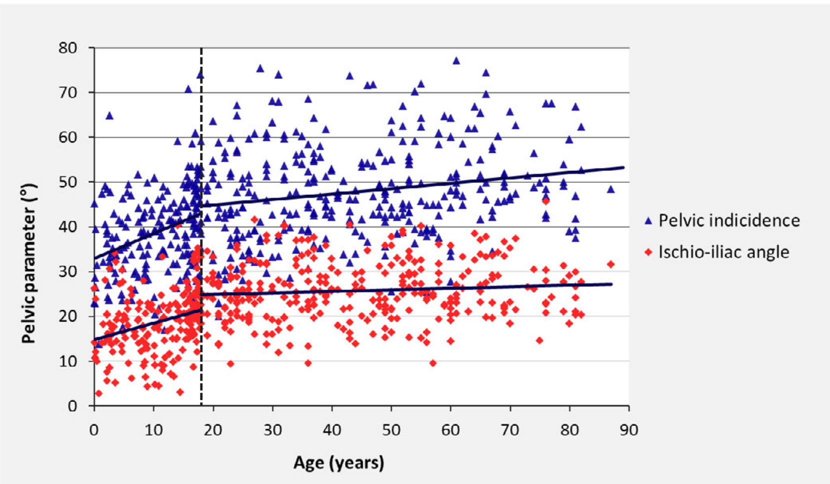


Figure 4. Ischio-iliac angle *versus* pelvic incidence (n=499). Pearson's correlation coefficient was *r*=0.558 (level of statistical significance *P*<0.001). Linear regression analysis revealed the formula ischio-iliac angle=0.4 × pelvic incidence + 6.3.



	parameter	*r*	*P*	Regression formula
< 18 years	Ischio-iliac angle	0.29	<0.001	= 0.4 * age +14.7
	Pelvic incidence	0.32	<0.001	= 0.6 * age +33.0
≥ 18 years	Ischio-iliac angle	0.10	0.046	= 0.0 * age +24.2
	Pelvic incidence	0.21	<0.001	= 0.1 * age +42.5

Figure 5. Ischio-iliac angle and pelvic incidence *versus* age in the pediatric (n=189) and adult (n=310) cohort. Ischio-iliac angle and pelvic incidence correlated significantly with age in pediatrics and in adults (*r*, correlation coefficient; *P*, level of significance).

DISCUSSION

A lordotic angulation between the ischial and iliac bone is a prerequisite for the unique way that humans ambulate, and for the subsequent unique biomechanical loading of the human spine.[10, 60] Although this angulation has been described before, this is the first study to quantify this angle in detail using computerized method in 499 humans of different ages.[10, 60] It demonstrated that:

1. Sagittal pelvic morphology parameters, ischio-iliac angle and pelvic incidence, increase significantly during pediatric growth and become relatively constant during adulthood;
2. A wide range of ischio-iliac angles as well as pelvic incidences was observed. Given the high reliability of the measurement method, the wide range of ischio-iliac angle (3-46°) and pelvic incidence (14-77°) in our population apparently represents the wide natural variation of pelvic morphology in the normal population, which is common for most spino-pelvic parameters;[18, 115]
3. There is a positive linear relation between ischio-iliac angle and pelvic incidence:
4. Given the relationship between the ischio-iliac angulation and pelvic incidence, and the earlier established relationship between the pelvic incidence and lumbar lordosis, ischio-iliac lordosis can be considered to be in harmonious continuity with the lumbar lordosis.[17, 20, 148]

In recent years, there has been an increasing recognition of the importance of the sagittal spino-pelvic alignment in relation to the functioning of the spine, and in the etiopathogenesis of different spinal pathologies.[5, 17, 18, 117, 125, 141-146] The role of the pelvis as a determinant and regulator of spinal alignment, to keep the spine optimally balanced, has also become increasingly apparent.[125, 146, 149]

The results of our study indicate that the sagittal alignment of the pelvis evolves during natural growth up to the end of the adolescent growth spurt. Previously, using two-dimensional radiographs, it was shown that the pelvic incidence increases slightly, thus altering sagittal spino-pelvic alignment during growth up to skeletal maturity.[17, 117, 118, 120] In more detail, Mangione et al. and Hanson et al. demonstrated in relatively small cohorts the difference between the pelvic incidence in fetuses, children and adults (with a mean pelvic incidence of 31° *versus* 39-47° *versus* 55-57°, respectively).[119, 150] Later, Mac-Thiong et al. confirmed these results in a cross-sectional population cohort of 341 children.[17, 117] Additionally, Mangione et al. and Mac-Thiong et al. reported a significant, but weak correlation of the pelvic incidence with age (r=0.36 and 0.21, respectively) and showed that the pelvic incidence increased +0.5-0.7° per year up to adulthood.[17, 117, 119] In the context of evolution, in 1998 Berge et al. reported the differences in length of the ilium in pelvises of 150 juvenile and adult primates, 60 human specimens and two early hominid pelvises. They showed that changes in pelvic proportions occur during growth and later life, and found that the two early hominid pelvises resemble pelvic morphology of human neonates. However, no sagittal pelvic parameters were quantified.[151] Recently, a study on the pelvic incidence in a historical collection of hominid pelvises, neonates and adults was published by Tardieu et al..[15] Using a 3-D landmark scanner, they found a higher pelvic incidence in 51 adults (54.5±12°) and seven early hominid pelvises (range, 43-54°), compared to 19 neonates (27.2±12.8°). Therefore, they concluded that the infantile pelvis is "mechanically poorly adapted to balance the trunk on the lower limbs". The results of our study, for which 3-D image reformation was used, are very consistent with the results of other studies on pelvic morphology of children at different ages. These studies, however, only looked at pelvic incidence.[17, 115, 118] Our study looks at the underlying anatomical adaptations and adds a quantification of the ischio-iliac angle at different ages. The lordosis between the ischium and ilium is an evolutionary trait of *homo sapiens* and is a prerequisite for our unique upright posture with a trunk that is delicately balanced straight above the pelvis.[10, 60] All other vertebrates, quadrupedal as well as bipedal, have their trunk in front of their hips, which leads to essentially different mechanical loading of the human spine, while the anatomy of the spine itself has remained essentially unchanged.[10, 60]

Although positional parameters such as the sacral slope, pelvic tilt and lumbar lordosis are influenced by positioning of the patients, morphological pelvic parameters such as the ischio-iliac angle and pelvic incidence are not. Therefore, due to the supine image acquisition of CT scans, these positional pelvic parameters could not be assessed. Neither could we evaluate the sagittal profile of the spinal curvature and its relation to pelvic incidence or ischio-iliac angulation. By using CT data and novel image processing techniques, we were able to quantify the ischio-iliac angle as well as the pelvic incidence on 3-D images with high accuracy and reproducibility in a large study population, as it was done for the pelvic incidence in a previous study.[147] Using this method, information bias and bias due to image acquisition was avoided. A strong positive correlation between the ischio-iliac angle and pelvic incidence was observed, which was also illustrated by the increasing ischio-iliac angle with the age of the subjects, synchronously with the increase of the pelvic incidence. Given the known correlation between the pelvic incidence and lumbar lordosis[17, 20, 148], the ischio-iliac lordosis apparently provides a harmonious continuity with a person's highly individual lumbar lordosis. The development of the ischio-iliac angle forms the anatomical basis for human upright spino-pelvic alignment. It aids our understanding of the differences in biomechanical loading of the human spine as compared to other vertebrates. It is not, however, a practical or clinically relevant parameter since it is impossible to measure it on plain radiographs.[152]

There is a large variation in sagittal spino-pelvic parameters in the population. Variation of the ischio-iliac angle and pelvic incidence, and thus sagittal spinal alignment, results in differences in biomechanical loading and functioning of the human spine.[18] In human evolution, the lordotic angulation of the pelvis in combination with the shortening of the ilium was a prerequisite for the unique human posture with the center of mass of the upper body straight over the pelvis. Simultaneously, the pelvic incidence increased to maintain the diameter of the bony birth canal.[15, 135, 148, 153] In this way, by keeping the ischium in a posterior orientation, the orientation and lever arm of the ischiofemoral and abductor muscles were preserved (Figure 1).[60, 154] Even in the oldest available pelvis of our hominid ancestors, the 3.2-million-year-old fossil of *Australopithecus afarensis*, popularly known as Lucy, an increased angulation between the ischium and ilium, and between the ischium and sacral bone (pelvic incidence) was found.[12] Human upright posture and bipedal ambulation, and therefore biomechanical loading of the human spine, thus differs considerably from other species, also other bipedal ones. In biomechanical experiments of Kouwenhoven et al. it was shown that the way the human spine is loaded implies a decrease in the rotational stiffness of certain spinal segments, thus being a risk factor for the development of idiopathic scoliosis. Sagittal alignment has also been implicated in other pathologies as spondylolisthesis and osteoarthritis of the hip, and has been suggested to play a role in low back pain.[145, 155]

In conclusion, an increasing ischio-iliac angle and pelvic incidence during normal growth was observed in this study. It displays a continuation of phylogenetic morphological changes of the human pelvis. It forms the basis for human upright spinal biomechanics, with possible consequences for the initiation and progression of idiopathic scoliosis, spondylolisthesis, Scheurmann's disease, degenerative disc disease or osteoarthritis of the hip.

Chapter 5

Analysis of Pre-existent Vertebral Rotation in the Normal Infantile, Juvenile, and Adolescent Spine

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ABSTRACT

Study Design. Vertebral rotation was systematically analyzed in the normal, non-scoliotic thoracic spine of children aged 0-16 years. Subgroups were created to match the infantile, juvenile, and adolescent age groups according to the criteria of the Scoliosis Research Society.

Objectives. To determine whether a distinct pattern of vertebral rotation in the transverse plane exists in the normal, non-scoliotic infantile, juvenile, and adolescent spine.

Summary of Background Data. We assume that, once the spine starts to deteriorate into a scoliotic deformity, it will follow a preexisting rotational pattern. Recently, we identified a rotational pattern in the normal non-scoliotic adult spine that corresponds to the most common curve types in adolescent idiopathic scoliosis. In infantile idiopathic scoliosis, curves are typically left-sided and boys are affected more often than girls, whereas in adolescent idiopathic scoliosis, the thoracic curve is typically right-sided and predominantly girls are affected. The present study is the first systematic analysis of vertebral rotation in the normal children's spine.

Methods. Vertebral rotation in the transverse plane of T2-T12 was measured using a semi-automatic method on 146 computed tomographic scans of children (0-16 years old) without clinical or radiological evidence of spinal pathology. Scans were mainly made for reasons such as recurrent respiratory infections, malignancies, or immune disorders. Vertebral rotational patterns were analyzed in the infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) boys and girls.

Results. In the infantile spine, vertebrae T2-T6 were significantly rotated to the left (P<0.001). In the juvenile spine, T4 was significantly rotated to the left. In the adolescent spine, T6-T12 were significantly rotated to the right (P=0.001). Rotation to the left was more pronounced in infantile boys than in girls (P=0.023). In juvenile and adolescent children, no statistical differences in rotation were found between the sexes.

Conclusions. These data support the hypothesis that the direction of the spinal curve in idiopathic scoliosis is determined by the built-in rotational pattern that the spine exhibits at the time of onset. The well-known predominance of right-sided thoracic curves in adolescent idiopathic scoliosis and left-sided curves in infantile idiopathic scoliosis can be explained by the observed patterns of vertebral rotation that preexist at the corresponding age.

INTRODUCTION

A typical feature of scoliosis is the interaction of vertebral rotation in the transverse plane and lateral deviation of the spine.[25] Vertebrae are always directed into the convexity of the lateral curve. In a recent computed tomographic (CT) study, we showed that in the normal, nonscoliotic spine the high thoracic vertebrae are rotated to the left and the mid and lower thoracic vertebrae to the right side.[25] Although considerably less in magnitude, this pre-existent rotational pattern in the non-scoliotic spine is comparable to the most prevalent types of adolescent idiopathic scoliosis (AIS), which are characterized by a right-sided main thoracic curve in which the mid/lower thoracic vertebrae are rotated to the right side and compensatory left-sided high thoracic and lumbar curves. It was hypothesized that, once AIS starts to develop due to a (to a large extent) still-to-be-determined cause, the direction of spinal curvature is determined by this already built-in rotational pattern. In contrast to AIS (10-16 years old), a high incidence (ranging from 56 to 88%) of left-sided thoracic curvatures are reported in infantile idiopathic scoliosis (0-3 years old).[156-158] In juvenile idiopathic scoliosis (4-9 years old) the number of left- and rightsided curves is about evenly divided.[159, 160] Given the hypothesis that the direction of the evolving scoliotic curve is determined by a pre-existent vertebral rotation at the time of onset, we hypothesize that at the infantile age, the normal thoracic spine shows a pre-existent pattern of rotation to the left side, at the juvenile age more or less neutral, and at the adolescent age to the right side.

SUBJECTS AND METHODS

Study population and computed tomography

A total of 539 children younger than 16 years who had undergone a CT scan of the thorax in our center between January 2005 and June 2009 for reasons such as recurrent respiratory tract infections, malignancies, or immune disorders were enrolled in this study. The scans were made with a Philips Brilliance 16-P CT scanner (Philips Healthcare, Eindhoven, The Netherlands) and the slice thickness varied between 4 and 5 mm. Exclusion criteria were clinical or radiologic evidence for trauma or spinal pathology, (e.g., a scoliosis with a Cobb angle larger than 10°), evidence for anatomical anomalies of internal organs, mental retardation or syndromes associated with disorder of growth, tumor in the spinal region, or a poor quality of the scan (i.e., <30 slices, artifacts, not fully transversal slices due to a skewed scan position). This led to the exclusion of 393 (73%) children; 64 (16%) had anatomical anomalies of the internal organs, 55 (14%) had spinal pathology or trauma; 58 (15%) had mental retardation or syndromes related with disorder of growth, 21 (5%) had a tumor in the spinal region. Furthermore, in 195

Table 1. Patients characteristics and scan indications of the infantile (0-3 years old), juvenile (4-9 years old) and adolescent (10-16 years old) cohorts.

	Inclusion		
	Infantile n=48	**Juvenile n=48**	**Adolescent n=50**
Age (SD)	1.9 (1.2)	7.2 (1.6)	13.3 (1.7)
Women(%)	22 (45.8)	20 (41.7)	18(36.0)
Scan indication:			
recurrent respiratory infections	19 (39.6)	20 (41.7)	10 (20.0)
malignancy	14 (29.2)	13 (27.1)	19 (38.0)
immune disorders	0 (0.0)	5 (10.4)	10 (20.0)
high fever	6 (12.5)	2 (4.2)	4 (8.0)
post-intervention	6 (12.5)	2 (4.2)	0 (0.0)
trauma	1 (2.1)	1 (2.1)	1 (2.0)
other	2 (4.2)	5 (10.4)	6 (12.0)

(50%) children the scan was of either too poor quality or consisted of too few slices. The resulting 146 children, 60 girls and 86 boys, were included in this study. Children were classified into the three age groups defined by the Scoliosis Research Society as infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old).[29]

Vertebral rotation of T2 down to T12 was evaluated in 48 infantile, 48 juvenile, and 50 adolescent children. Patient's characteristics and scan indications for each cohort are given in Table 1.

Computed tomographic measurement method

Vertebral rotation was measured in the transverse plane from T2 till T12 using the same CT measurement method as was used in our previous studies.[25, 27] This method consisted of a semi-automated procedure using an in-house created, interactive computer program to calculate the rotation angle of the vertebrae in a robust and reproducible way. Vertebral rotation was defined as the angle between the longitudinal axis of each vertebra and the midsagittal axis of the trunk. The mid-sagittal axis was defined as the line passing through the center of the spinal canal and center of the sternum at level T5, since at this level the sternum was most clearly visible. The longitudinal axis of each vertebra was defined as the line passing through the center of the spinal canal and the center of the anterior half of the vertebral body. After segmentation of the vertebrae, spinal canals and sternum at level T5, these points and, subsequently, the rotation angles of the vertebrae were calculated fully automatically. The reference line was defined as zero-degrees rotation. From a caudal view, anti-clockwise rotation of the vertebrae (rotation of the vertebral body to the right side of the subject) was defined

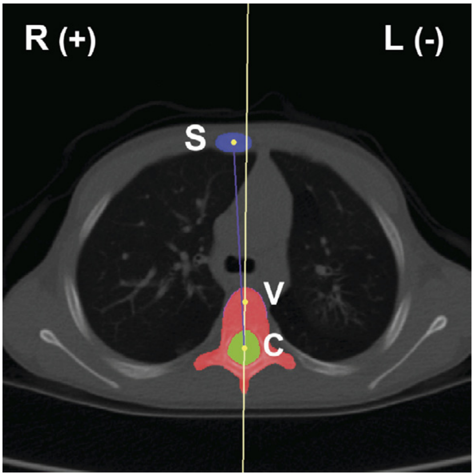

Figure 1. CT slice at level T5 in the transverse plane. Vertebral rotation was defined as the angle between the mid-sagittal axis (line between the center of the sternum (S) and the center of the spinal canal (C)) and the longitudinal axis of the vertebra (line through the anterior half of the vertebral body (V) and spinal canal (C)).

as a positive angle, rotation to the left side (clockwise) as a negative angle (Figure 1). The vertebrae, spinal canal, and sternum were semi-automatically segmented by three experienced observers (M.M.A.J., J.W.M.K., and T.P.C.S.). The intraclass correlation coefficients calculated for inter- and intraobserver reliability of this method were 0.96 ± 0.06 and 0.99 ± 0.01 (mean ± SD), respectively.[25]

Statistical analysis

The statistical analysis was performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL). One-sample t tests were used to evaluate the significance of vertebral rotation on each vertebral level. A *P* value of 0.005 was considered to be statistically significant for the one-sample t tests since this test was performed 11 times (Bonferroni's correction). Repeated measures analysis of variance was used to analyze the differences between age cohorts and between the genders within each age cohort. The statistical significance level for repeated measures analysis of variance was set at 0.05 or less.

RESULTS

The mean vertebral rotation for each level in the different age groups is demonstrated in Table 2 and Figure 2. In all age cohorts a preexisting pattern was observed in which the high thoracic vertebrae were more rotated to the left side than the mid and lower thoracic vertebrae. At the infantile age, the mean vertebral rotation was to the left side

Table 2. Analysis of the vertebral rotation in non scoliotic children showed significant rotation to the left in infantile children (0-3 years old) and in juvenile children (4-9 years old) and to the right in adolescents (10-16 years old). Mean vertebral rotation angles and 95% confidence intervals are in degrees. Significant measurements are marked with *. The significance level was set at 0.005 due to a Bonferroni correction.

Age (years old)			**Vertebral level**										
			T2	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**
0-3 n=48		Mean	−1.6	−2.0	−2.3	−1.8	−1.3	−0.6	−0.6	−0.9	−1.1	−1.1	−1.1
	95% CI	Lower	−2.4	−2.8	−3.0	−2.5	−2.0	−1.4	−1.4	−1.7	−2.0	−2.2	−2.2
		Upper	−0.7	−1.2	−1.6	−1.1	−0.6	0.1	0.3	−0.1	−0.1	0.0	0.0
		P	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.107	0.169	0.025	0.027	0.047	0.056
4-9 n=48		Mean	−0.2	−0.8	−1.7	−1.0	0.3	0.7	0.5	0.7	0.3	0.2	0.0
	95% CI	Lower	−0.9	−1.5	−2.4	−1.8	−0.5	−0.2	−0.4	−0.2	−0.6	−0.7	−1.0
		Upper	0.5	−0.1	−0.9	−0.1	1.1	1.5	1.3	1.6	1.2	1.1	1.0
		P	0.612	0.035	<0.001*	0.032	0.487	0.142	0.294	0.132	0.531	0.607	0.980
10-16 n=50		Mean	0.7	−0.9	−1.2	−0.1	1.4	1.8	1.7	1.9	1.9	2.1	1.4
	95% CI	Lower	−0.2	−1.6	−2.0	−0.8	0.7	1.0	0.9	1.1	1.1	1.3	0.6
		Upper	1.5	−0.2	−0.4	0.7	2.1	2.6	2.5	2.7	2.7	2.8	2.2
		P	0.111	0.016	0.005	0.873	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.001*

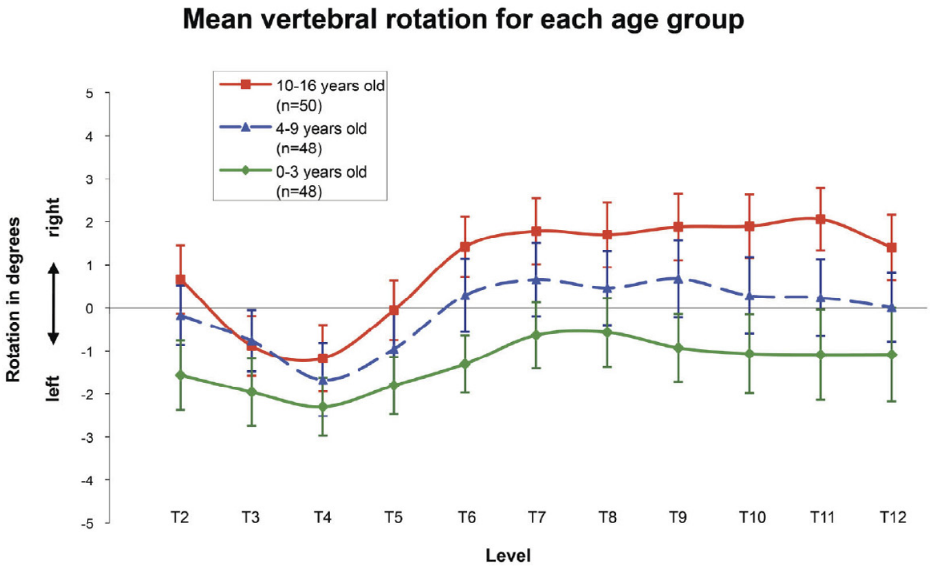

Figure 2. Vertebral rotation in the transverse plane (mean and 95% confidence interval) of T2-T12 in the infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) non-scoliotic children. All measurements are in degrees.

at all thoracic levels. This was significant at T2-T6 (P<0.001). In juvenile children, T4 was significantly rotated to the left side (P<0.001). Other thoracic vertebrae were not significantly rotated to either side. At the adolescent age T4 was significantly rotated to the left side (P=0.005) and T6-T12 were significantly rotated to the right side (P=0.001).

Effect of age

Repeated measures analysis (with the within-factor vertebral level and between-factors age and sex) showed a main effect of age on the vertebral rotation. The differences between the rotational patterns of the adolescent- and the infantile-age cohort and between the infantile and juvenile-age cohort were shown to be statistically significant, P<0.001 and P=0.045, respectively. The difference between the juvenile- and the adolescent-age cohort was not statistically significant (P=0.056).

Effect of sex

Mean vertebral rotation in three cohorts for both boys and girls is shown in Table 3 and Figure 3. In infantile boys, mean vertebral rotation was left-sided on all levels of which T2-T6 were statistically significant (P<0.001). In infantile girls, level T4 was significantly rotated to the left side (P=0.001). The rotational pattern in the infantile boys and girls was significantly different (P=0.023). The rotational pattern in boys was more rotated to the left side than in girls. No statistically significant differences were found between

Table 3. Analysis of the vertebral rotation in non scoliotic boys and girls showed significant rotation to the left in infantile boys and girls (0-3 years old) and in juvenile boys and girls (4-9 years old) and to the right in boys and girls (10-16 years old). Mean vertebral rotation angles and 95% confidence intervals (95% CI) are in degrees. Significant measurements are marked with *. The significance level was set at 0.005 due to a Bonferroni correction.

Age (years old)			Vertebral level										
			T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Boys													
0-3 n=26		Mean	−2.6	−2.3	−3.0	−2.6	−2.1	−1.4	−1.3	−1.5	−1.7	−1.9	−1.9
	95% CI	Lower	−3.7	−3.5	−4.0	−3.7	−3.0	−2.6	−2.4	−2.6	−3.1	−3.5	−3.6
		Upper	−1.4	−1.1	−1.9	−1.6	−1.1	−0.2	−0.1	−0.4	−0.4	−0.3	−0.3
		P	<0.001*	0.001*	<0.001*	<0.001*	<0.001*	0.024	0.037	0.009	0.016	0.024	0.023
4-9 n=28		Mean	−0.2	−0.8	−1.6	−1.1	0.5	0.7	0.9	1.2	0.8	0.7	0.3
	95% CI	Lower	−1.2	−1.8	−2.5	−2.1	−0.6	−0.5	−0.3	−0.1	−0.4	−0.5	−1.0
		Upper	0.8	0.2	−0.7	−0.1	1.6	1.8	2.1	2.4	2.0	1.9	−1.6
		P	0.693	0.107	0.001*	0.036	0.333	0.269	0.153	0.065	0.209	0.239	0.643
10-16 n=32		Mean	0.7	−1.0	−1.5	−0.3	1.5	1.7	1.5	1.6	1.6	1.9	1.5
	95% CI	Lower	−0.3	−1.9	−2.4	−1.0	0.7	0.7	0.5	0.7	0.7	1.1	0.5
		Upper	1.8	0.0	−0.6	0.4	2.3	2.7	2.4	2.4	2.5	2.7	2.5
		P	0.162	0.043	0.003*	0.444	<0.001*	0.001*	0.003*	0.001*	0.001*	0.000*	0.004*
Girls													
0-3 n=22		Mean	−0.4	−1.6	−1.5	−0.9	−0.4	0.3	0.2	−0.3	−0.3	−0.2	0.1
	95% CI	Lower	−1.4	−2.7	−2.3	−1.5	−1.3	−0.6	−0.9	−1.5	−1.6	−1.6	−1.4
		Upper	0.7	−0.4	−0.8	−0.1	0.5	1.2	1.4	1.0	1.0	1.2	1.5
		P	0.465	0.008	<0.001*	0.020	0.326	0.554	0.687	0.672	0.630	0.790	0.939
4-9 n=20		Mean	−0.2	−0.7	−1.8	−0.8	0.0	0.7	−0.1	0.0	−0.4	−0.4	−0.4
	95% CI	Lower	−1.1	−1.8	−3.1	−2.4	−1.4	−0.8	−1.4	−1.3	−1.8	−1.9	−2.2
		Upper	0.8	0.4	0.4	0.9	1.3	2.1	1.3	1.3	1.1	1.0	1.4
		P	0.758	0.189	0.013	0.339	0.947	0.352	0.888	0.994	0.608	0.546	0.629
10-16 n=18		Mean	0.5	−0.7	−0.6	0.3	1.3	1.9	2.1	2.5	2.5	2.3	1.2
	95% CI	Lower	−0.9	−1.9	−2.2	−1.3	−0.3	0.5	0.6	0.7	1.1	0.7	−0.5
		Upper	1.9	0.4	0.9	1.9	2.9	3.4	3.5	4.2	3.9	3.9	2.9
		P	0.453	0.206	0.411	0.674	0.102	0.011	0.008	0.008	0.002*	0.006	0.143

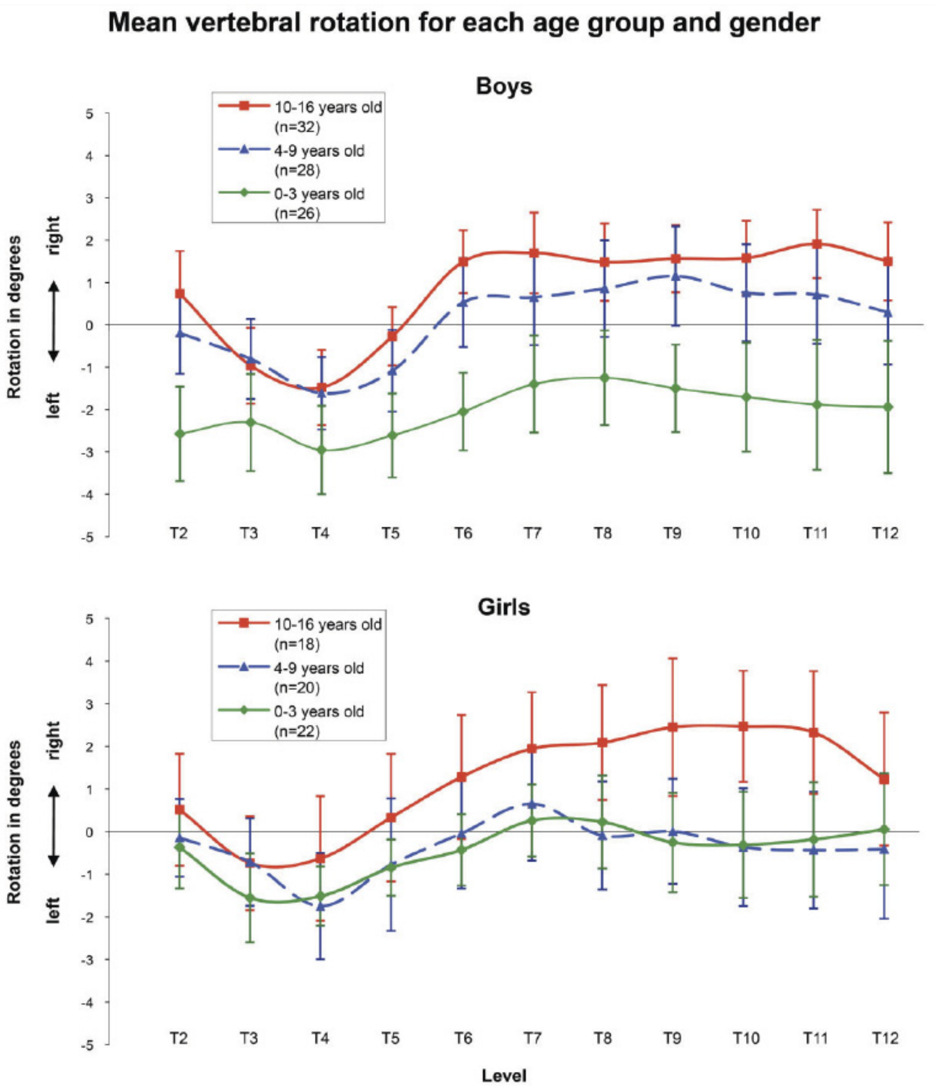

Figure 3. Vertebral rotation in the transverse plane (mean and 95% confidence interval) of T2-T12 in the infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) non-scoliotic boys and girls. All measurements are in degrees.

the sexes in the juvenile- and adolescent-age cohorts (*P*=0.485 and *P*=0.810, respectively).

DISCUSSION

Many theories about the etio-pathogenesis of idiopathic scoliosis have evolved in the literature since the beginning of the last century.[2] Despite a tremendous body of gained knowledge on the subject, answers to a number of relevant questions are still lacking. In the present study we addressed the question why thoracic curves are usually right-sided in AIS and left-sided in infantile idiopathic scoliosis.

Analysis of vertebral rotation in the normal, non-scoliotic spine showed that the mid and lower thoracic spine was rotated to the left side at the infantile age, was not significantly rotated to either side at the juvenile age, and was rotated to the right side at the adolescent age. The observed pattern at the adolescent age was comparable to the pattern observed in our previous systematic analysis of vertebral rotation in the spine in an adult population.[25] The authors earlier hypothesized in this previous study that the direction of the developing curve in AIS is determined by a rotational pattern already present in the spine before the spine starts to develop the deformity. The results of the present study support this hypothesis for different age groups that are known to exhibit different curve patterns.[156-158, 160-162]

James et al. subdivided idiopathic scoliosis into infantile, juvenile, and adolescent types, based on the time of onset.[156, 161, 162] This classification is still being used by the Scoliosis Research Society.[29] They, and others[157, 158, 160], showed that at the infantile age, thoracic idiopathic scolisis is more frequently left convex and most often affects boys. In contrast, in AIS the thoracic curve is more right convex and girls are more affected than boys. The differences in vertebral rotation found in the present study match the rotational pattern of thoracic idiopathic scoliosis in different age groups.[156-158, 160-162]

At the infantile age, mean vertebral rotation of the thoracic vertebrae was significantly more pronounced to the left side in boys than in girls. Although pre-existent rotation occurs in every individual and even in quadrupeds[27] (and thus can never be the cause of scoliosis) it is noteworthy that this difference matches the higher incidence of infantile idiopathic scoliosis in boys. A sex-related difference in magnitude of rotation was not observed at the adolescent age.

As in our previous CT studies,[25, 27] we used the mid-sagittal axis as a reference line, which was defined as the line passing through the center of the spinal canal and the center of the sternum at the level of T5. We used this definition as this line showed to be a good representation of the anatomical midline of the trunk and the used reference points have a very high reproducibility.

Obviously, the study population consisted of hospitalized children, for whom an indication for a CT examination of the thorax existed. We tried to avoid the influences of underlying diseases in this population, by broadly excluding children with disorders that possibly affect the normal development of the spine. In that sense, there is no reason to believe that the rotation patterns found in this study would differ from the healthy population. No ethics committee would however allow a similar CT study in normal children, and even magnetic resonance imaging would be difficult to execute because of the long scan times that would probably require anesthesia in the younger children.

Many anatomists already recognized that the normal spine is never straight or symmetrical.[1] In a previous study, we showed a relation between the asymmetrical position of the thoracic organs and pre-existent vertebral rotation, as persons with a situs inversus totalis appeared to have a pre-existent pattern of vertebral rotation opposite to what is seen in humans with normal organ anatomy.[24] Taylor et al.[54] hypothesized that the eccentric position of the thoracic aorta might be responsible in the development of this pre-existent rotational tendency as, according to Hueter-Volkmann, asymmetrical pressure of the aorta on the neurocentral cartilage might result in an asymmetrical pedicle growth. More in general, the organ asymmetry that exists in both the thorax and the abdomen can be inferred to play a role in the direction of this pre-existent rotation.

Our results suggest that the preexisting left-sided rotation at the infantile age converts into a right-sided rotation at some point in time during growth; all vertebrae are rotated to the left at the infantile age, whereas most mid and lower thoracic vertebrae are rotated to the right at the adolescent age. Why rotational patterns are present and differ between age groups is not answered by this study, but in line with our previous investigations, it may be related to differences in organ mass at different ages.

Questions regarding the etio-pathogenesis of idiopathic scoliosis are not answered by this study either. This study does, however, give an explanation for the well-known phenomenon of predominance in curve direction at the various ages.

CONCLUSION

This study showed that there is a pattern of pre-existent vertebral rotation in the normal, nonscoliotic spine that depends on age. At the infantile age, rotation is predominantly to the left; at the adolescent age, it is to the right; and at the juvenile age, no significant rotation to either side is found. At the infantile age, mean vertebral rotation was more to the left in boys than in girls. These results match the direction of the curve in infantile, juvenile, and adolescent idiopathic scoliosis and support the hypothesis that the direction of the curve in idiopathic scoliosis is determined by the rotational pattern present in the normal spine.

Chapter 6

Quantitative analysis of the closure pattern of the neurocentral junction as related to pre-existent rotation in the normal immature spine

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ABSTRACT

Background. The normal spine is not a symmetrical structure. In recent studies we demonstrated the presence of an axial rotational pattern that is similar to what is seen in the most prevalent curve patterns in idiopathic scoliosis at different ages. This suggests that, if the spine starts to decompensate into scoliosis, it follows this pre-existent rotational pattern. In scoliosis, the NCJs close asymmetrically, which leads to a different pedicle morphology in the convexity and concavity of the curve. The present study aimed to establish at which age the NCJ closes in different regions of the spine, whether it closes asymmetrically in the non-scoliotic spine as well, and whether the closure pattern is related to the earlier demonstrated pre-existent rotation.

Purpose. To evaluate the closure pattern and surface area of the left and right neurocentral junctions (NCJs) throughout the normal immature spine, in relation to pre-existent spinal rotation at different ages.

Design. Retrospective cohort study using a systematic, semi-automatic analysis.

Patient sample. CT scans of the thorax and abdomen of 199 non-scoliotic children (0-16 years old) were systemically analyzed. CT scans had been obtained for several reasons unrelated to this study, e.g. recurrent respiratory infections, malignant disease (not involving the spine), or work up prior to bone marrow transplantation. Scans were categorized according to the criteria of the Scoliosis Research Society into an infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) age cohort.

Outcome measures. Closure, absolute surface area, and the angle between the longitudinal axis and the left and right NCJ, and pre-existent vertebral rotation at each spinal level.

Methods. Transverse CT slices were systemically analyzed for closure and asymmetry of the absolute area of 4992 NCJs from spinal levels T2 to L5. The outcome measures were analyzed semi-automatically, using custom made software developed at our institution (ImageXplorer, Image Sciences Institute). Inter- and intra-observer reliabilities were calculated.

Results. For all subjects, the entire thoracic area was available. Complete scans down to L5 of the lumbar spine were available in 43 cases. Closure of the NCJs was first observed in the lumbar spine, then in the high thoracic spine, and finally in the mid- and low thoracic spine. Closure occurred asymmetrically, left-right predominance depended on age. In the mid- and low thoracic spine, the surface areas of the right NCJs were larger at the infantile age, whereas at the juvenile age the areas of the left NCJs were larger. This corresponded to the spine's pre-existent rotation. Rotation of the high thoracic vertebrae was to the left in all age cohorts. Rotation in the mid- and low thoracic spine was to the left in the infantile cohort, but reversed to the right in the juveniles, and even more so in the adolescents. The lumbar spine was rotated to the left at the infantile age,

and not significantly rotated at the juvenile and adolescent age. Orientation of the NCJs in relation to the vertebras' longitudinal axis was symmetrical, not dependent on age and more transverse at mid-thoracic levels than at other spinal levels.
Conclusions. This study focuses on the asymmetry and regional pattern of closure of the NCJs at different ages. It suggests that pre-existent rotation of the spine is related to the asymmetrical closure of the NCJs. Whether the asymmetry is the cause of, or is caused by the pre-existent rotation cannot be derived from this study.

INTRODUCTION

The normal spine is not a symmetrical structure, as has been appreciated for a long time.[1, 163-165] More recently, we confirmed the presence of an axial rotational pattern that depends on age. This rotational pattern is identical in direction -although less in magnitude- to the rotation that occurs in idiopathic scoliosis in different regions of the spine and at different ages. Apparently, once the spine starts to decompensate into scoliosis, it follows this pre-existent rotational pattern.

The neurocentral junctions (NCJs) of the vertebrae connect the pedicles and laminae to the vertebral body bilaterally, and allow for growth in radial direction of the spinal canal. Asymmetric growth and closure of the NCJs occurs in the development of pathological rotation of the spine, as is known in naturally occurring scoliosis as well as in experimental scoliosis. The timing and order at which the NCJs close in the normal, non-scoliotic spine is still under debate. Its relation to axial rotational patterns in the normal spine has not been established to the best of our knowledge. The aim of the present study was to analyze the closure patterns of the NCJs throughout the normal growing spine in relation to pre-existent spinal rotation at different ages.

SUBJECTS AND METHODS

Between 2005 and 2011, 755 children of the Dutch population under 16 years of age underwent CT scanning of their thorax and abdomen for several indications unrelated to this study, e.g. recurrent pulmonary infections, immune disorders, or prior to bone marrow transplantation, at the University Medical Center in Utrecht, the Netherlands. All medical information that has been documented in the electronic patient record, prior and after the CT examination, were reviewed for the in- and exclusion criteria. A total of eighty children with spinal pathology or spinal trauma and 23 children with a tumor in the spinal region were excluded. Other exclusion criteria were anatomical abnormalities

Table 1. Subject characteristics for the infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) cohorts are shown. The infantile, juvenile, and adolescent subgroups were created using the classification of the Scoliosis Research Society.[166]

	Infantiles 0-3 years old		Juveniles 4-9 years old		Adolescents 10-16 years old	
n	52		69		78	
Age in years (SD)	2.1	(1.1)	6.7	(1.6)	13.6	(1.7)
Women (%)	20	(38)	25	(36)	27	(35)
Patients who underwent CT-thorax (%)	44	(85)	53	(77)	59	(76)
Patients who underwent CT-thorax and CT-abdomen (%)	8	(15)	16	(23)	19	(24)
Scan indication:						
Recurrent pulmonary infections (%)	22	(42)	28	(41)	21	(27)
(Suspected) malignancy	10	(19)	15	(22)	26	(33)
Trauma	7	(13)	13	(19)	15	(19)
Immune disorder	5	(10)	7	(10)	12	(15)
High fever	5	(10)	1	(1)	2	(3)
Post-intervention	2	(4)	3	(4)	0	(0)
Other	1	(2)	2	(3)	2	(3)

of internal organs (89 children), and syndromes affecting growth (77 children). In addition to exclusion by scan indication, 287 children were excluded because CT images consisted of too few (<25) slices, had too poor quality or showed artifacts. Thus, 199 children (26% of the original group) were available for evaluation; 127 boys and 72 girls. Characteristics and scan indications are shown in Table 1. All children had at least good quality scans of their thoracic region. Frequently, thoracic scans also included levels L1 (n=118) and L2 (n=72). In total, forty-three children had undergone CT examination of the abdomen as well, and were thus available for evaluation of both their complete thoracic as well as their lumbar spine. All scans were made with a Philips Brilliance 16-P CT-scanner (Philips Medical Systems B.V., Best, the Netherlands). Pixel size varied between 0.25 and 0.50mm and slice thickness between three and five mm.

Orientation and closure patterns of the NCJs, as well as vertebral axial rotation, were evaluated in these 199 children, divided into three age cohorts according to the definition of the Scoliosis Research Society (SRS).[166] There were fifty-two (26%) children between 0 and 3 years old (infantile), sixty-nine (35%) between 4 and 9 (juvenile) and seventy-eight (39%) between 10 and 16 (adolescent).

CT Measurement Method

All measurements were performed semi-automatically, using in-house developed software (ImageXplorer, Image Sciences Institute). Of all vertebrae, the mid-vertebral transverse slice, on which the pedicles were best visible, was selected. Measurements were performed at each available spinal level. Two types of measurements were performed:

I. Pre-existent vertebral rotation.
II. Closure, absolute surface area and orientation of the left and right NCJ.

ad I: At each spinal level, segmentation of the vertebra and spinal canal was performed. To evaluate the vertebral rotation at each spinal level, the same measurement method was used as in our previous studies; the intraclass correlation coefficient (ICC) for inter- and intraobserver reliability was 0.96 ± 0.06 and 0.99 ± 0.01 (mean ± SD), respectively. With this method, vertebral rotation was defined as the angle between the longitudinal axis of the vertebra and a midline through the thorax in the transverse plane (Figure 1). After segmentation, the centre of mass (COM) of the spinal canal and anterior half of the vertebra were automatically calculated. The longitudinal axis of the vertebra was calculated by a line through the COM of the spinal canal and the COM of the anterior half of the vertebra. The midline through the thorax was calculated by a line through the COM of the canal and the COM of the sternum at level T5. Vertebral rotation to the left was defined as negative and to the right as positive.

ad II: First, at each spinal level the left and right NCJs were determined as being open or closed. NCJ was defined as open when there was a low density zone on the CT scan

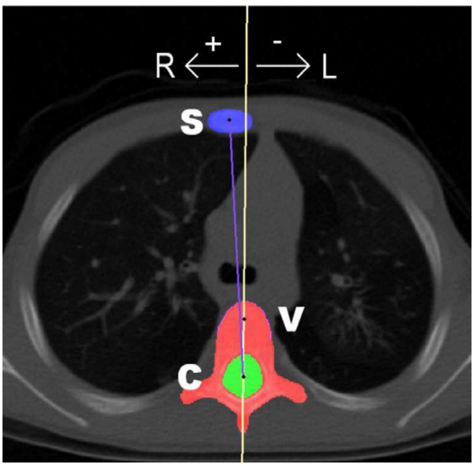


Figure 1. Vertebral rotation - the angle between the longitudinal axis of the vertebra (spinal canal 'C' – center of mass anterior half of the vertebra 'V') and a midline through the thorax (spinal canal 'C' – sternum 'S') - was semi-automatically measured on the transverse slices of CT-scans of normal children.

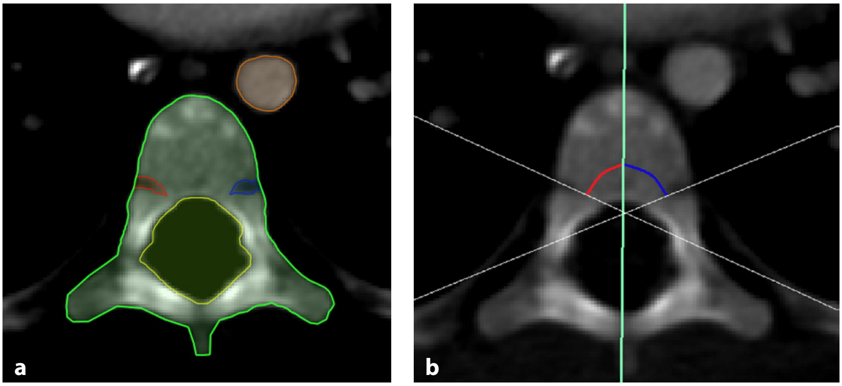


Figure 2. a: Segmentation of the vertebra, spinal canal, and the NCJs; b: The angle between longitudinal axis of the vertebra and neurocentral junction was calculated for the right side (*in red*) and left side (*in blue*).

between two regions with high density, similar to the density of the vertebral cortex. Open NCJs were manually segmentated, which included partial volume effects: small NCJs consisting of only partial pixels were also segmentated. The window level was standardized on bone window setting. A total of 4992 NCJs, divided over the three age cohorts and sixteen spinal levels, could be analyzed. Age of closing of the NCJ was, in line with Rajwani *et al*, defined as the age at which fifty percent of the NCJs were closed at each spinal level. After segmentation of all open NCJs (Figure 2a), absolute surface area data of all NCJs in square millimeters were determined automatically. Next, two best-fit lines were drawn through the NCJs at each level (Figure 2b). To investigate the relation between the direction of a vertebra and the orientation of the NCJs, we calculated the angle between the longitudinal axis of the vertebra — as previously defined — and the corresponding NCJ line.

Interrater agreement for binominal data was calculated using Cohen's kappa coefficient. Intraclass correlation coefficient (ICC) for inter- and intraobserver reliability, including 95% confidence intervals (95%CI), were calculated for continuous data.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL). Repeated measures ANOVA with Greenhouse-Geisser significance was used to evaluate differences in continuous data between the age cohorts. Because of the correlation of data of different spinal levels within a single subject, intersegment differences and left/right differences were defined as within factors; age cohort and gender as between factors. For *post hoc* analyses, a Bonferroni correction was applied. To test the relation between NCJ asymmetry and the rotational direction, Pearson's chi-square was used. For all tests a P value <0.05 was considered to be statistically significant.

RESULTS

NCJ closure

NCJs closure starts at lumbar levels L1-L3. At an average age of 4-5 years, 50% of all NCJs at these vertebral levels were closed in both boys and girls. Thereafter, closure spreads to high thoracic levels and lower lumbar levels L4-L5 at the age of 6-7 years for both genders. Closure finishes in the mid- and low thoracic spine at the age of 6-9 years in girls and 7-11 years in boys (Figure 3).

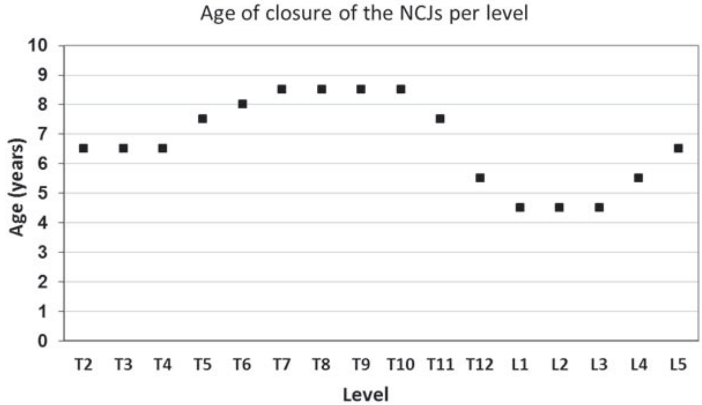


Figure 3. The average age is shown at which >50% of the neurocentral junctions were closed on the analyzed CT-slices of normal children.

The mean surface area of the NCJs showed comparable results. Repeated Measures ANOVA showed that the surface area of the NCJs was dependant on age, spinal level and gender. The mean surface area of NCJs was 7.2mm^2 (95%CI: 6.9-7.3) in infantiles, 2.6 mm^2 (2.4-2.8) in juveniles, and 0.5mm^2 (0.5-0.6) in adolescents (Figure 4). At the adolescent age, 90% of NCJs were completely closed. The 10% of NCJs that were determined to be still open, had a mean surface area of less than 1.0 mm^2.

As can be expected from the age of closure, the NCJs had a larger surface area at mid- and low thoracic levels as compared with high thoracic and lumbar levels at the same age (P=0.009) (Figure 4). The mean surface area of the NCJs throughout the spine was larger in boys than in girls in all age cohorts (P=0.019).

NCJ asymmetry

The surface areas of the left and right NCJs were asymmetrical throughout the spine. In the thoracic spine at the infantile age, the right NCJ was predominantly larger than the left, whereas at the juvenile age, the left NCJ was predominantly larger than the right.

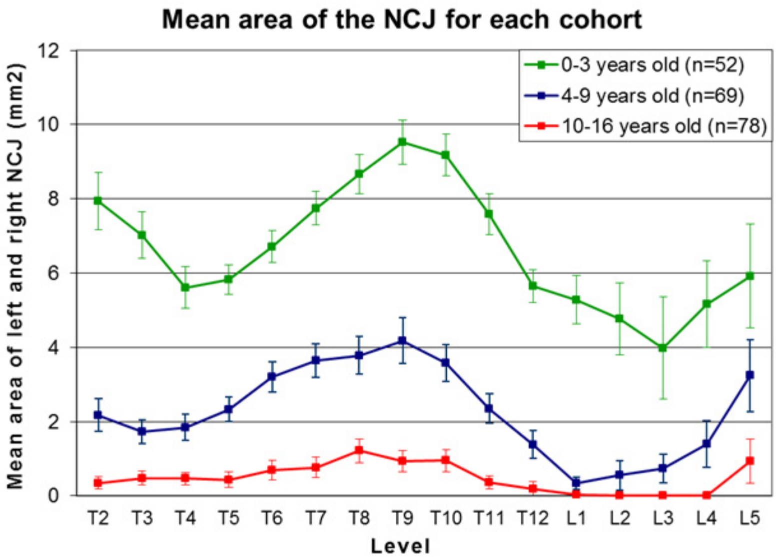


Figure 4. Mean surface areas of the left and right NCJs at each spinal level from T2 to L5 are shown for the infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) cohorts. Error bars indicate the standard error.

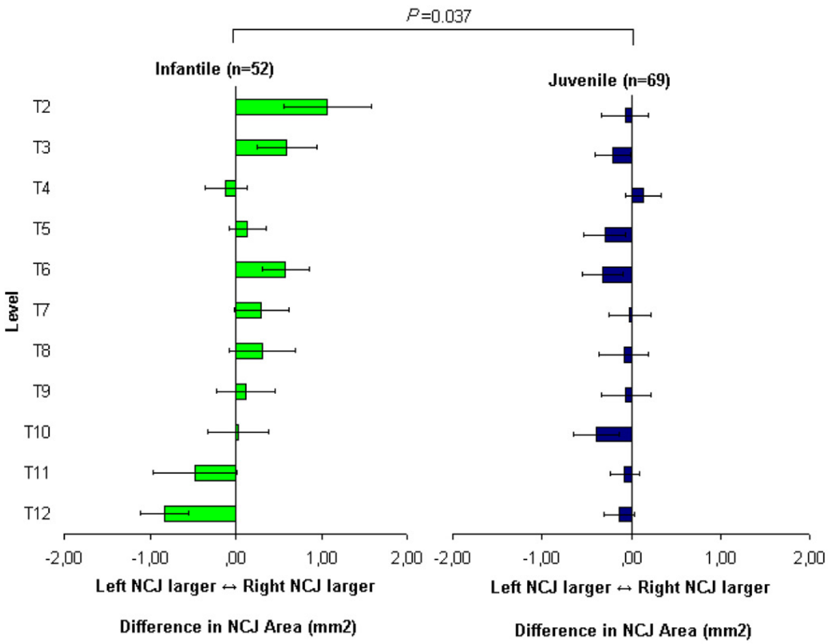


Figure 5. Asymmetry in NCJ area was defined as the mean surface area of the right NCJ minus the surface area of the left NCJ. Therefore, positive values of the left-right difference in NCJ surface area indicate levels at which the right NCJ is larger and vice versa. The graph shows the mean differences in NCJ surface area for each spinal level in the infantile and juvenile cohorts. Error bars indicate the standard error.

Post hoc analysis showed that the differences in NCJ asymmetry were largest between the infantile and juvenile age cohorts (P=0.037) (Figure 5). At the adolescent age, most levels (90%) were symmetrically closed. No significant differences in NCJ asymmetry were found between the genders at any age.

NCJ orientation

The angle between the longitudinal axis of the vertebra and the NCJs was symmetrical and not dependent on age. The NCJs showed a more horizontal orientation on transverse CT slices at the mid-and low thoracic levels than at high thoracic levels and lumbar levels in all age cohorts (P=0.001) (Figure 6).

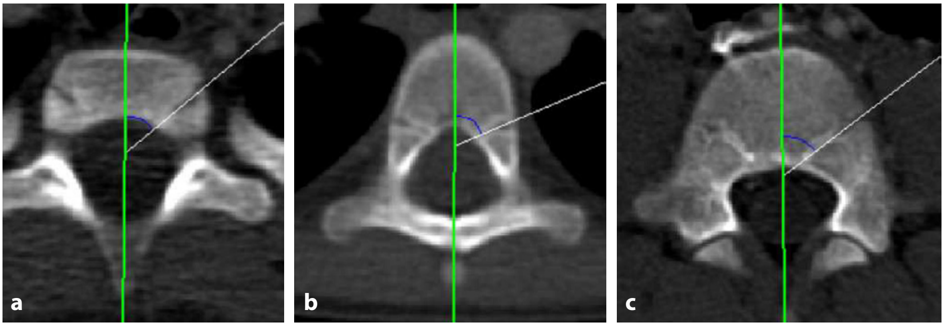


Figure 6. The neurocentral junctions showed a more transverse orientation at the mid-thoracic levels (b) than at high thoracic levels (a) and lumbar levels (c) in all age cohorts.

Pre-existent rotation

Mean vertebral rotation was significantly different between the age cohorts as well (P<0.001) (Figure 7). The spinal column was globally rotated to the left at all spinal levels of infantile children (P≤0.05). At the juvenile age, level T3 was rotated to the left (P=0.001) and levels T7, T8 and T10 to the right (P≤0.035). Other thoracic and lumbar levels were not significantly rotated at the juvenile age. At the adolescent age, levels T3 and T4 were still rotated to the left (P≤0.007), levels T6 to T12 to the right (P≤0.004) and the spine reverted back to neutral around the thoracolumbar junction.

Furthermore, at the juvenile age, at the levels T4, T6, T7 and T10, there was a significant relation between the larger NCJ (left *versus* right) and the direction of axial rotation (P=0.009, P=0.004, P=0.003, P=0.017, respectively). A larger right NCJ was associated with axial rotation to the left, and a larger left NCJ with rotation to the right at these levels. This relation was not statistically significant at the other spinal levels and age cohorts.

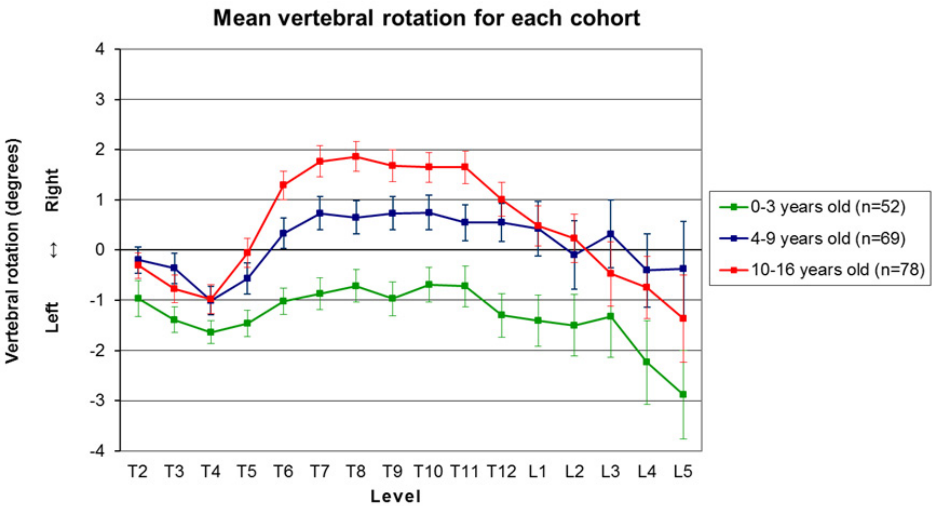


Figure 7. Mean vertebral rotation angles on each spinal level are shown for the infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) cohorts. All age cohorts showed rotation to the left at high thoracic levels (T2-T4). At mid- and low thoracic levels T6-T12, infantile children showed rotation to the left, juveniles to the right, and adolescent more to the right. Rotation to the left was defined as negative and to the right as positive. Error bars indicate the standard error.

Reproducibility

Interrater agreement on the closure of the NCJs was calculated according to Cohen's kappa: 0.92 ± 0.06 (mean ± standard error). ICC for inter- and intra-observer reliabilities were 0.96 (95%CI: 0.95-0.96) and 0.99 (95%CI: 0.98-1.00) for the absolute surface area measurements and 0.85 (95%CI: 0.80-0.88) and 0.88 (95%CI: 0.85-0.91) for the angle measurements, respectively.

DISCUSSION

This study provides an in-depth analysis of NCJ closure patterns related to age, gender, spinal level, left *versus* right side and pre-existent spinal rotation. Knowledge of the closure patterns of the NCJ during growth at different spinal levels is important for several reasons:

1. The employment of transpedicular screw osteosynthesis has become a standard procedure, potentially leading to premature growth arrest and spinal canal stenosis if performed at an age when that particular NCJ is still very active.
2. Closure of the NCJ has been shown to occur asymmetrically in scoliosis.[1, 164, 165] In order to determine whether this constitutes pathology, knowledge of closure patterns in the non-scoliotic spine is essential.

3. Forced asymmetrical closure by unilateral screw epiphysiodesis has been shown to lead to scoliosis-like deformity in experimental animal models.

The asymmetrical closure of the NCJs in the normal mid- and low thoracic spine is consistent with the pre-existent rotational patterns at the infantile, juvenile, and adolescent age. In the mid- and low thoracic spine of infantiles, the right NCJs were predominantly larger and the spine was rotated to the left; whereas in the mid- and low thoracic spine of juveniles, the left NCJ was predominantly larger and the spine was rotated to the right. The mid- and low thoracic spine of adolescents was rotated to the right, most NCJs were already closed and thus unavailable for analysis.

The patterns of pre-existent rotation that we described previously in the normal spine at different ages were confirmed by this study.[25, 26, 167] We are not aware of any other study that analysed asymmetry of the NCJ in relation to spinal rotation throughout the spine in this semi-automatic, systematic manner. Taylor reported asymmetry of the NCJs in a cadaver study of normal, infantile and juvenile spines, based on observations only.[54] More recently, Zhang *et al.* did not observe asymmetry in the length and width of the NCJs of thirty-four paediatric patients without spinal deformity.[55]

Age of closure of the NCJ appeared to be dependent on spinal level. In the literature, the age and sequence of closure of the NCJs has been discussed in a number of studies. Different study designs have been used, which might account for seemingly conflicting results. Rajwani *et al.* studied the closure of the NCJs in the thoracic spine in the sagittal plane with magnetic resonance imaging (MRI). In our study, an identical definition for the age of closure was used as in the studies of Rajwani *et al.*: the age at which 50% of the NCJs are closed. They reported that closure of the NCJs in the thoracic and lumbar spine takes place between ten and fifteen years of age. In our study, closure of the NCJs was observed at a much earlier age, between four and nine years old, which may be accounted for by the differences between CT and MRI in analysing cartilaginous structures.

Additionally, this study demonstrated that the spinal levels with the larger NCJs close at a later age than levels with smaller ones. Thus, surface area may be considered a measure of remaining epiphyseal activity, which suggests that larger NCJs will continue to grow longer than smaller ones. The mean NCJ surface areas in our study were larger in boys than in girls, which may indicate the later closure in boys than in girls in accordance with their later skeletal maturity.

Zhang *et al.* concluded that NCJ development is "age- and vertebral level-dependant".[55] In our study, the same sequence of spinal regions with closing NCJs were observed as Vital *et al.* and Zhang *et al.* reported earlier: The normal sequence of ossification of the NCJ starts at the lumbar levels, followed by high thoracic levels. The ossification of the NCJs in the mid- and low thoracic spine occurred last in these studies. However, Rajwani *et al.* reported contrasting results. They showed that high thoracic levels close later than the mid- and low thoracic spine. The major differences of the age and sequence of closure of the NCJs might - at least partly - be explained by several differences in study methods.

Firstly, for the epiphyseal plates in the peripheral skeleton, it has been reported that closure spreads in specific directions. For example, the ossification of the epiphyseal plate of the distal tibia expands slowly from anteromedial to posteriolateral.[168] Rajwani *et al.* and Zhang *et al.* observed in MRI and cadaver studies, respectively, that ossification of the NCJs starts in the middle of the NCJ and then expands into the superior and inferior parts of the growth plate. In the present study, CT images of the transverse plane were used. It was repeatedly observed that an NCJ was determined as closed on the selected slice, while more cranially or caudally the NCJs were still open. To evaluate both vertebral rotation and NCJ closure, we performed analyses on the transverse, midvertebral slices, where the pedicles were best visible. From first signs of ossification of the growth plates, it might take months to years before the whole epiphyseal plate is closed.[168] Our results represent the age of closure of the NCJs at mid-pedicular level and might therefore differ from the results of studies performed in the sagittal plane.

Secondly, the other investigators used MR images in the sagittal plane, or cadaver specimens of Eskimos. In addition to the plane of analysis, the radiological technique may explain the variability in the reported age of closure. Recent MRI studies showed later age of closure than CT and cadaver studies. In epiphyseal trauma it is well known that MRI provides additional information as compared with CT by imaging of the phases prior to growth plate closure.[169]

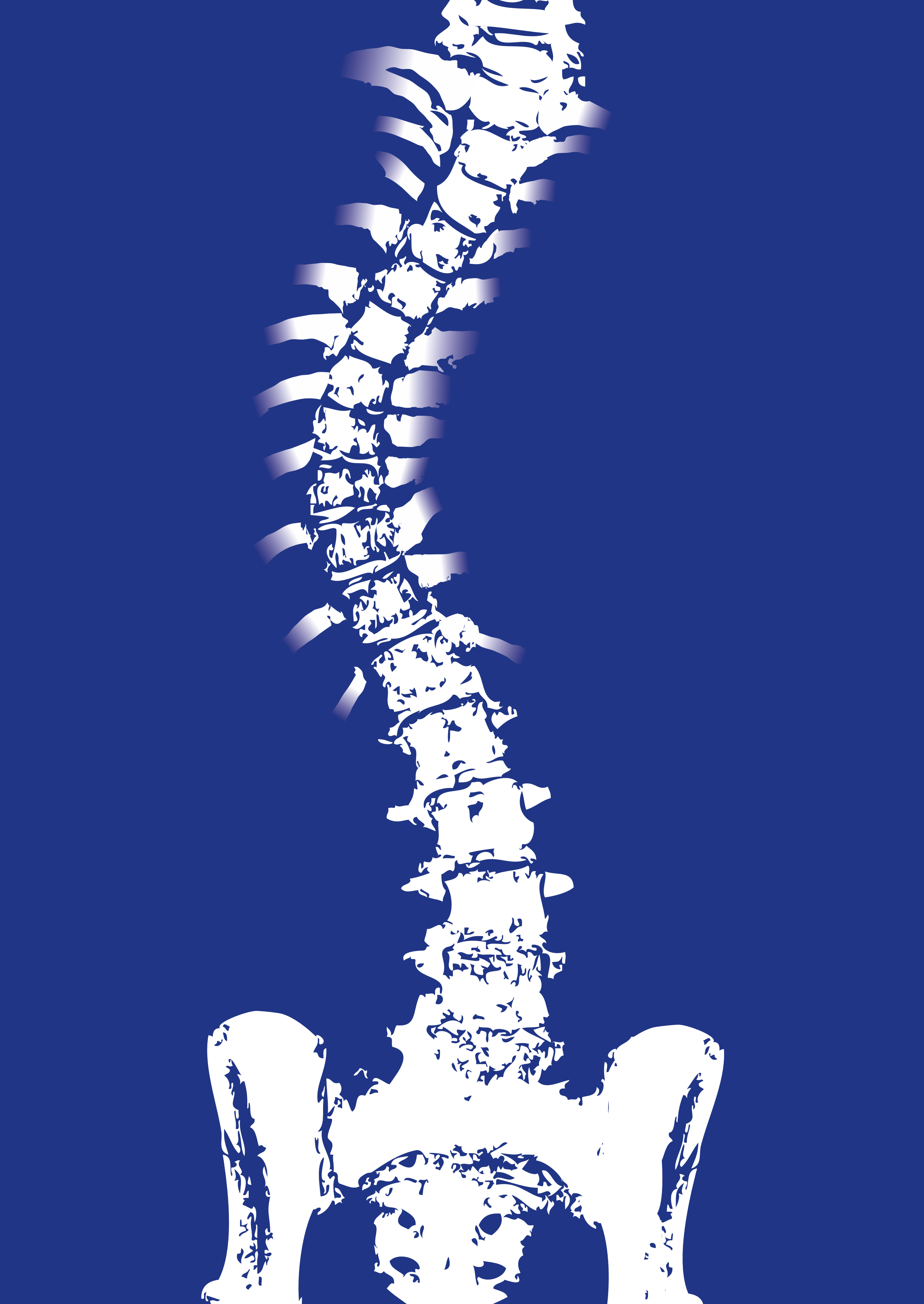
Thirdly, racial differences might explain the differences in the literature. Interracial differences in the age of closure of epiphyseal plates have been reported by Crowder and Austin, and Gilsanz *et al*.[170, 171] They showed that complete ossification of the epiphyseal plates occurs at an earlier age in Mexican-American and African males than in European-American males. Zhang *et al.* reported the age of closure of the NCJs in 34 Eskimo skeletons, Rajwani *et al.* in a Canadian population, and our study was performed in a Dutch population of paediatric patients. This variability of race within the study populations might partly explain the differences in age of closure.

This study does not answer the question whether NCJ asymmetry causes the spinal rotation, or is a consequence of a rotation that is caused by other factors. From the peripheral skeleton it is known that growth plates may unilaterally be more active, leading to usually negligible — but sometimes significant — leg length discrepancies. In analogy with the peripheral skeleton, a disturbance of this normally harmonious and symmetrical mechanism could lead to a discrepancy in pedicle length, progressive rotation and possibly scoliosis, similar to what was demonstrated in experimental scoliosis by several investigators. In this study, the larger NCJ was related to the direction of axial rotation at thoracic spinal levels at the juvenile age. These results are consistent with the studies reporting NCJ asymmetry in scoliosis patients. Vital et al. showed that asymmetry of the NCJs in a scoliotic population results in a lengthening of the pedicle on the concave side, as was also demonstrated by Nicoladoni and Taylor at an earlier stage. If NCJ asymmetry is its cause, some still unknown mechanism must influence neurocentral epiphyseal activity at the different ages.

On the other hand, Hueter Volkmann's law implies accelerated closure of the epiphysis under compression, and delayed closure under distraction.[172, 173] Therefore, the changes in pre-existent rotation and NCJ asymmetry in the immature spine might be caused by another mechanism. During development of the child, the spine is subject to changes in mechanical load by motor development and physical growth (stature, weight, and shift in body proportions). In this study no differences in axial rotation of the vertebrae between children of 0 to 18 months old (which are generally not able to stand and walk alone[174]) and 18 months to 3 years old (which are generally able to stand and walk alone) were observed, retrospectively. We previously showed that pre-existent rotation is related to organ anatomy[24], and therefore the described changes in NCJ asymmetry could very well be a passive phenomenon.

CONCLUSION

This study demonstrates that age of closure of the NCJ depends on spinal level, that left-right asymmetry depends on age and gender, and that asymmetry corresponds to the earlier demonstrated (and in this study confirmed) rotational patterns that preexist in the normal, non-scoliotic spine. Whether the asymmetry is the cause of, or is caused by the pre-existent rotation or is the cause of the convexity of the curve in idiopathic scoliosis cannot completely be derived from this study. This requires a longitudinal study set-up, focussed on the early changes in the three-dimensional morphology of the spine in an immature population at risk for development of idiopathic scoliosis.

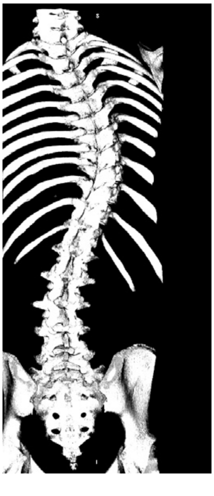


Part II

Adolescent Idiopathic Scoliosis

Chapter 7

Differences in early Sagittal Plane Alignment between Thoracic and Lumbar Adolescent Idiopathic Scoliosis



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Runner-up Outstanding Paper Award 2013

ABSTRACT

Background context. It has previously been shown that rotational stability of spinal segments is reduced by posteriorly directed shear loads that are the result of gravity and muscle tone. Posterior shear loads act on those segments of the spine that are posteriorly inclined, as determined by each individual's inherited sagittal spinal profile. Accordingly, it can be inferred that certain sagittal spinal profiles are more prone to develop a rotational deformity that may lead to idiopathic scoliosis; and lumbar scoliosis, on one end of the spectrum, develops from a different sagittal spinal profile than thoracic scoliosis on the other end.
Purpose. To examine the role of sagittal spinopelvic alignment in the etio-pathogenesis of different types of idiopathic scoliosis.
Study design/setting. Multicenter retrospective analysis of lateral radiographs of patients with small thoracic and lumbar adolescent idiopathic scoliotic curves.
Patient sample. We included 192 adolescent idiopathic scoliosis patients with either a thoracic (n=128) or lumbar (n=64) structural curve with a Cobb angle of less than 20° were studied. Children with other spinal pathology or with more severe idiopathic scoliosis were excluded, because this disturbs their original sagittal profile. Subjects who underwent scoliosis screening and had a normal spine were included in the control cohort (n=95).
Outcome measures. Thoracic kyphosis, lumbar lordosis, T9 sagittal offset, C7 and T4 sagittal plumb lines, pelvic incidence, pelvic tilt, and sacral slope, as well as parameters describing orientation in space of each individual vertebra between C7 and L5 and length of the posteriorly inclined segment.
Methods. On standardized lateral radiographs of the spine, a systematic, semi-automatic measurement of the different sagittal spinopelvic parameters was performed for each subject using in-house developed computer software.
Results. Early thoracic scoliosis showed a significantly different sagittal plane from lumbar scoliosis. Furthermore, both scoliotic curve patterns were different from controls, but in a different sense. Thoracic kyphosis was significantly decreased in thoracic scoliosis compared with both lumbar scoliosis patients and controls. For thoracic scoliosis, a significantly longer posteriorly inclined segment, and steeper posterior inclination of C7-T8 was observed compared with both lumbar scoliosis and controls. In lumbar scoliosis, the posteriorly inclined segment was shorter and located lower in the spine, and T12-L4 was more posteriorly inclined than in the thoracic group. The lumbar scoliosis cohort had a posteriorly inclined segment of the same length as controls, but T12-L2 showed steeper posterior inclination. Lumbar lordosis, pelvic incidence, pelvic tilt, and sacral slope, however, were similar for the two scoliotic subgroups as well as the controls.
Conclusions. This study demonstrates that even at an early stage in the condition, the sagittal profile of thoracic adolescent idiopathic scoliosis differs significantly from

lumbar scoliosis, and both types of scoliosis differ from controls, but in different aspects. This supports the theory that differences in underlying sagittal profile play a role in the development of different types of idiopathic scoliosis.

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional rotatory deformity of the spine.[1] It has previously been shown that the human spine, in a rotational sense, is a much less stable construct than any other spine in nature, because rotational stiffness of spinal segments is decreased by posteriorly directed shear loads.[26, 167] These posteriorly directed shear loads are the result of gravity and muscle tone, they are unique for bipedal man and act on all posteriorly inclined segments of the spine as determined by each individual's unique sagittal profile (Figure 1). Accordingly, it can be inferred that the

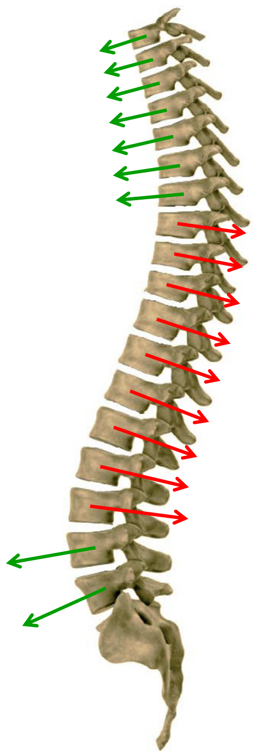

Figure 1. In the erect human spine, all vertebrae are exposed to axial compression, but in addition, certain areas are subject to posteriorly directed shear loads (arrows in red), others to anterior shear loads (green arrows), depending on their spatial orientation. Posteriorly directed shear loads render the segment less rotationally stable as compared to anterior shear loads.[6]

area of the spine in which a rotational deformity has a chance to develop, is based on differences in the sagittal profile. In other words, scoliosis can be expected to develop on a different sagittal profile than a nonscoliotic spine, and lumbar scoliosis can be expected to develop on a different sagittal profile than thoracic scoliosis. In order to investigate this, sagittal profile differences must be determined at a very early stage of the condition, since more advanced scoliosis, by nature of its three-dimensional deformity, in itself causes changes in the sagittal alignment of the spine.

In this retrospective multicenter study, the sagittal spino-pelvic alignment of small thoracic scoliosis was compared to similar lumbar curves. Furthermore, sagittal profiles of both curve types were compared with controls without scoliosis.

SUBJECTS AND METHODS

Population

Following Institutional Review Board approval, all patients between 10 and 16 years old with the ICD-9-code for idiopathic scoliosis who had had standard postero-anterior (PA) and lateral radiographic evaluations of the spine in one of two major scoliosis centers (Nemours, Alfred I duPont Hospital for Children, Wilmington, Delaware, United States and University Medical Center Utrecht, Utrecht, The Netherlands) between January 2006 and December 2011 were enrolled in this study. A flow-chart for inclusion and exclusion is shown in Figure 2. Only patients with either a single thoracic or a single lumbar coronal curve of less than 20 degrees were included in this study. All children with radiographs

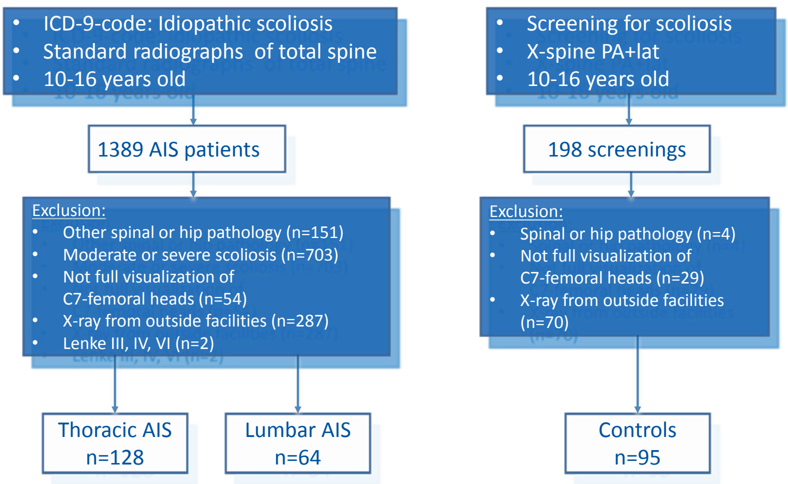

Figure 2. In- and exclusion flowchart. PA = postero-anterior.

of poor quality, radiographs from outside facilities or on which the whole spine from C7 to S1 and both femoral heads were not clearly identifiable were excluded.

A control cohort was created by selection of all children who had undergone standard radiographic screening for scoliosis because of school nurse or general practitioner referrals or own initiative of the parents, but had no scoliosis documented clinically or radiographically. Exclusion criteria for this group of children were the same. Demographics were collected for all included subjects and compared between the cohorts.

Radiography

In both centers, as recommended by the Scoliosis Research Society, plain full-length radiographs were made in an upright standing position, with anterior superior iliac spines and hips parallel to the cassette and the beam aimed at T10.[175] General Electric AL01F (General Electric, Schenectady, NY, USA), Philips Digital Diagnost (Philips B.V., Best, The Netherlands) and Siemens VERTIX (Siemens, Erlangen, Germany) were used for digital radiography. Lateral radiographs were made with the patient in a position as similar as possible to the AP radiograph, with the beam 90 degrees to that used for AP radiography, with anterior superior iliac spines and hips perpendicular to the film and with the right side of the patient to the cassette. Subjects were instructed to look straight forward and to stand in a relaxed manner with arms flexed forward at 45 degrees, hands supported on poles in one center, or fingertips on zygomatic bones in the other center, to maintain a neutral sagittal stance.

Measurement of spino-pelvic parameters

Similar to a previous study[23], two trained observers (resident orthopedic surgery and orthopedic research student) used in-house developed software to measure a number of sagittal spino-pelvic parameters semi-automatically: thoracic kyphosis, lumbar lordosis, T9 sagittal offset, C7 and T4 sagittal plumb lines, pelvic tilt, pelvic incidence, sacral slope as well as inclination of each individual vertebra between C7 and L5 and length and inclination of, and number of vertebrae included in the posteriorly inclined segment (Figure 1). All sagittal spino-pelvic parameters of this study including abbreviations and exact descriptions are shown in Table 1. Before segmentation of each vertebra - by indication of its four angles, and three points on the femoral head contours (Figure 3) - all lateral radiographs were randomized and the observers blinded for demographics and spinal alignment on the AP radiograph. Centroids of each vertebra and hip-axis (HA) were calculated automatically. Because of the variety in height in normal adolescents, normalization was performed for all distance parameters by dividing the distance by the total length of C7 to the sacrum, thus providing a proportion rather than an absolute length. For C7 and T4 sagittal plumb lines, positive values were assigned for anterior

Table 1. An overview of the nomenclature, abbreviations and descriptions of all sagittal spino-pelvic parameters is shown.

	Spinal balance parameters	Abbreviation	Definition
Spinal parameters	Thoracic kyphosis	TK	Constrained Cobb angle between lines drawn along the superior endplate of T4 and the inferior endplate T12.[179]
	Lumbar lordosis	LL	Constrained Cobb angle between lines drawn along the superior endplates of L1 and the sacral endplate.[179]
	C7/T4 Sagittal plumb line	C7HA/T4HA	Distance between the plumb lines passing through midpoint between the centers of both femoral heads and the plumb lines from the centroids of the C7 and T4 vertebral bodies, normalized for C7-S1 length.
	T9 sagittal offset	T9SO	Angle between the vertical and the line connecting the centroid of T9 vertebral body to the hip axis.
Pelvic parameters:	Pelvic tilt	PT	Angle between the line connecting the midpoint of the sacral plate to the hip axis, and the vertical.
	Pelvic incidence	PI	Angle between the perpendicular to the sacral plate and the line connecting the sacral endplate midpoint to the hip axis.
	Sacral slope	SS	Angle between the superior endplate of S1 and the horizontal.
Inclination of the spine	Vertebral inclination	VI	Angle between the inferior endplate of a vertebra and the horizontal.
	Declive length	DL	Length of posteriorly inclined segment, normalized for C7-S1.
	Declive inclination	DI	Angle between a line through the centroids of the cranial and caudal end level of the posteriorly inclined segment and the vertical.
	Number of declive vertebrae	#DV	Number of vertebrae in the thoracic or lumbar spine of which the inferior endplate is posteriorly inclined.

displacement. Positive values for vertebral inclination indicate anterior inclination, negative values posterior inclination.

Despite the fact that the inter- and intraclass correlation coefficients (ICC) for all parameters were calculated in a previous study and proved to be reliable, ICC's and 95%CI were calculated once again for this study population.[23] Reliability analysis was performed by the two independent observers on a subgroup of ten randomly selected subjects.

Statistical analysis

The statistical analyses were performed using statistical software SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for the cohorts, providing means and standard deviations for continuous data and frequencies, percentages and medians for nominal data. Normality of age-distribution within the cohorts was tested using Kolmogorov-Smirnov tests. Demographical differences between the cohorts were analyzed using analysis of variance (ANOVA) and Chi-square.

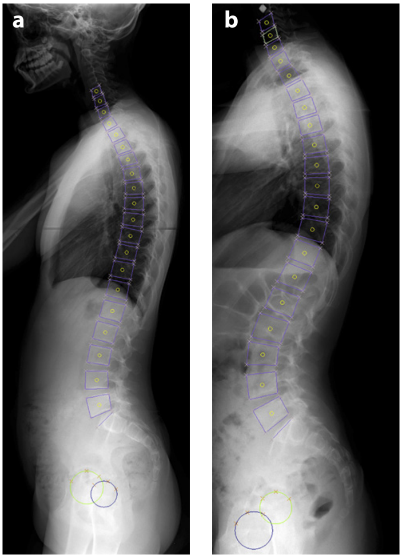

Figure 3. Measurements using the SpinIX software. Radiographs of a thoracic scoliosis (a) and lumbar scoliosis case (b) are shown in the graphical user interface of the in-house developed software. After indicating the four angles of each vertebra and three points on the femoral head contours the centroids of the vertebral bodies and the hip-axis were calculated automatically.

Chi-square was used to compare the number of posteriorly inclined vertebrae between the cohorts. For continuous parameters indicating general spino-pelvic alignment, ANOVA was performed to compare the three cohorts. For vertebral inclination of C7-L5, first, multivariate analysis of variance (MANOVA) was performed to reduce the type-1-error rate. Second, a significant MANOVA was followed by individual ANOVA's in order to see the effect of inclination of each individual vertebra on sagittal alignment. Significant ANOVA's were followed by a *post-hoc* test and Bonferroni's correction was applied. For vertebral inclination, a P value of <0.05 was considered to be statistically significant. Since eleven different general spino-pelvic parameters were compared in the same subjects, the significance level was adjusted to <0.005 for the general spino-pelvic parameters.

RESULTS

Population

Out of a total database of 1389 AIS patients, 128 patients with small (< 20 degrees) thoracic scoliosis and 64 with lumbar scoliosis of the same magnitude were included in this study. Ninety-seven controls were eligible for inclusion; see Figure 2 for the inclusion algorithm. The control patients had no scoliosis on clinical and radiographic examinations,

Table 2. Patient characteristics and curve types are shown for the three cohorts. SD=standard deviation.

Demographic parameter		Thoracic scoliosis (n=128)	Lumbar scoliosis (n=64)	Controls (n=95)
Mean age (SD)		13.0 (±1.8)	13.6 (±1.7)	13.0 (±1.8)
Women		95 (74%)	48 (75%)	58 (61%)
Cobb angles (°)[39]		10-20	10-20	<10
Lenke curve type	1A or 2A	89 (70%)		
	1B or 2B	37 (29%)		
	1C or 2C	2(2%)		
	5		64 (100%)	

they had been given the recommendation to return to the facility if any sign or symptom of scoliosis appeared. Two subjects developed scoliosis after the radiography and were excluded from the control population. Of all other controls, none had returned at the time of the study (mean follow-up of 2.7 years at an age of 15.7 years old). Ultimately, in this study, sagittal spino-pelvic alignment of 128 patients with thoracic scoliosis could be compared to 64 lumbar scoliotics and 95 control subjects. Age was evenly and normally distributed in the cohorts and no differences in age, gender or Risser's sign were observed between the cohorts (Table 2).

Spinal and pelvic parameters

Thoracic kyphosis was significantly less in thoracic scoliosis ($P<0.001$), and significantly greater in lumbar scoliosis as compared to controls ($P<0.001$). C7 was positioned more posteriorly in thoracic scoliosis compared to controls ($P<0.001$). Lumbar lordosis, T4 plumb line and T9 sagittal offset, pelvic incidence, pelvic tilt and sacral slope, were not significantly different between the cohorts (Table 3 and 4, Fig 3 and 4).

Posteriorly inclined segment

In the thoracic group, the posteriorly inclined segment was significantly longer and consisted of more vertebrae than in the lumbar group or in controls ($P<0.001$ for all four tests). On the contrary, for lumbar scoliosis, the posteriorly inclined segment was shorter, but showed a steeper posterior inclination compared to thoracic scoliosis and to controls ($P<0.001$ and $P=0.002$, respectively). The length and number of vertebrae that formed the posteriorly inclined segment did not differ significantly between lumbar scoliosis and controls (but it, as stated above, its posterior inclination angle was steeper).

Table 3. Parameters indicating global sagittal spino-pelvic alignment are shown. Nomenclature, abbreviations and descriptions of the different parameters are shown in Table 1. A *P* value <0.005 was considered statistically significant. n.s. = not significant.

	Sagittal spino-pelvic parameter	Thoracic scoliosis (n=128)	Lumbar Scoliosis (n=64)	Controls (n=95)	*P*
General spinal parameters	TK (°)	27.6 (±8.0)	41.9 (7.5)	34.9 (9.4)	<0.001
	LL (°)	53.9 (10.1)	56.7 (11.3)	53.7 (10.1)	n.s.
	C7HA (ratio)	11 (12)	7 (12)	5 (9)	<0.001
	T4HA (ratio)	18 (11)	17 (10)	14 (8)	n.s.
	T9SO (°)	7.8 (5.9)	9.4 (4.3)	7.8 (3.6)	n.s.
Pelvic parameters	PT (°)	8.5 (8.2)	5.0 (8.8)	5.6 (8.3)	n.s.
	PI (°)	47.0 (11.8)	41.9 (10.6)	43.3 (12.9)	n.s.
	SS (°)	39.1 (7.9)	36.9 (8.4)	37.7 (8.6)	n.s.
Declive segment parameters	DL (ratio)	79 (9)	67 (10)	68 (10)	<0.001
	DI (°)	13.8 (4.4)	17.9 (4.0)	15.4 (4.9)	<0.001
	#DV (median)	10	8	8	0.001

Table 4. Significance of *post hoc* tests are shown for each sagittal spino-pelvic parameter. Nomenclature, abbreviations and descriptions of the different parameters are shown in Table 1. n.a. = not applicable, based on insignificant ANOVA for that specific parameter. n.s. = not significant *post hoc* test. The significance level was set at <0.005.

	Thoracic scoliosis *versus* lumbar scoliosis	Thoracic scoliosis *versus* controls	Lumbar scoliosis *versus* controls
Parameter	***P***	***P***	***P***
TK	<0.001	<0.001	<0.001
LL	n.a.	n.a.	n.a.
C7HA	n.s.	<0.001	n.s.
T4HA	n.a.	n.a.	n.a.
T9SO	n.a.	n.a.	n.a.
PT	n.a.	n.a.	n.a.
PI	n.a.	n.a.	n.a.
SS	n.a.	n.a.	n.a.
DL	<0.001	<0.001	n.s.
DI	<0.001	n.s.	0.002
#DV	<0.001	<0.001	n.s.

Spacial orientation of each individual vertebra

After equality of co-variance of vertebral inclination between the cohorts and vertebral levels was evident, significant differences in vertebral inclination between the cohorts was found. For the thoracic group, levels C7 to T8 were significantly more posteriorly in-

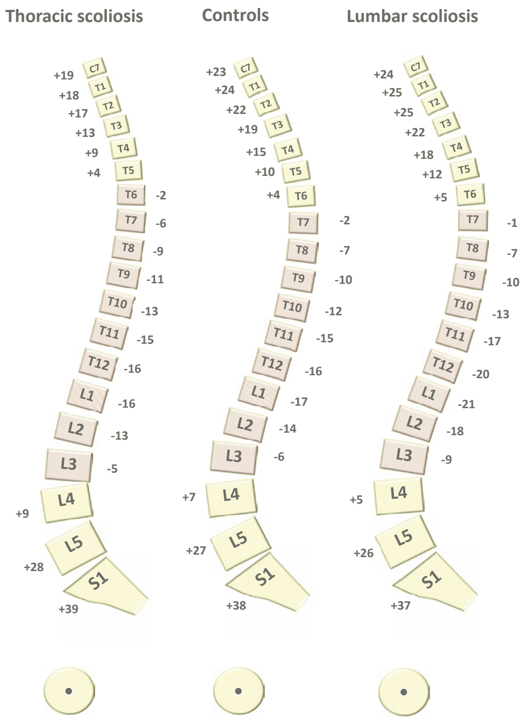

Figure 4. Mean inclination of the vertebrae in three cohorts. The configuration of the spine was illustrated using mean vertebral inclination and mean normalized sagittal plumb lines of each spinal level in relation to the hip-axis and horizontal, respectively.

clined as compared to the lumbar group. On the other hand, T12 to L4 showed a steeper posterior inclination in the lumbar scoliosis group. No significant difference between the AIS subtypes was observed in the inclination of levels T9 to T11, or the position of L5. As opposed to the controls, the C7-T8 segments were more posteriorly inclined in thoracic scoliosis, however, in lumbar deformities, the T2-T4 segment showed more forward inclination, whereas T12-L2 was more posteriorly inclined.

Reproducibility

ICC for inter- and intra-observer reliabilities for all angle measurements were 0.96 (95%CI: 0.77-1.00) and 0.94 (95%CI: 0.85-0.98) for general sagittal spino-pelvic parameters; 0.98 (95%CI: 0.96-0.99) and 0.96 (95%CI: 0.91-0.98) for normalized distance measurements; and 0.99 (95%CI: 0.98-0.99) and 0.99 (95%CI: 0.98-0.99) for vertebral inclination, respectively. ICC for inter- and intra-observer reliability for locating the corners of the vertebra was 0.99 (95%CI: 0.99-1.0) and 0.99 (95%CI: 0.99-1.0), respectively. The mean difference between the location of the corners of each individual vertebra between two different measurements and two different observers was 1.0±0.7mm and 1.4±0.7mm, respectively.

DISCUSSION

Human upright spinal biomechanics is unique and is known to play an important role in the development and progression of idiopathic scoliosis.[5, 30, 136, 176] Previously, it has been demonstrated that posteriorly directed shear loads, that uniquely act on those segments of the human spine that are posteriorly inclined, lead to a decrease in rotational stiffness of these exposed spinal segments (Figure 1).[6] The area on which these destabilizing loads act is determined by the individual's inherited sagittal spinal profile, which is known to be rather variable, especially during growth.[115, 117, 118] In our concept of idiopathic scoliosis, this decrease in rotational stiffness determines which vertebrae are prone to develop a true rotational instability of certain areas of the spine, i.e. idiopathic scoliosis with its different curve patterns.

If the vertebrae that will engage in this rotatory deformity are indeed the ones in a biomechanically 'destabilized area', it can be inferred that the sagittal profile of the scoliotic spine differs from the normal spine, and that different coronal curve patterns are preceded by differences in sagittal profile, already in the early stages of development of the curvature. It would be ideal to have information on the sagittal profile of the growing spine before the onset of the deformity, but obviously, this would require a large prospective population study with upright imaging of the spines of a large number of growing children, of whom only a small proportion would ultimately develop a scoliosis. This could resolve the question of whether these children have a different sagittal profile from the ones that do not develop a scoliosis, and whether different curve patterns show different sagittal morphology already early on. Since it seems practically and ethically very difficult to perform such a study using ionizing radiation in a growing population, we performed what we considered "second best" in order to shed light on this question. We compared the sagittal profile of three groups: patients with established, but small thoracic scoliosis, patients with lumbar scoliosis of the same magnitude, and controls without scoliosis.

Table 3 and 4, and Figure 3 show that the sagittal spino-pelvic alignment of thoracic idiopathic scoliosis differs significantly from lumbar scoliosis, and that both types of scoliosis differ from controls. Thoracic kyphosis was smallest in thoracic scoliosis and largest in the lumbar scoliosis group. In thoracic scoliosis, C7 to T8 was more posteriorly inclined and the posteriorly inclined segment longer than in lumbar scoliosis and controls, while in lumbar scoliosis the segment T12-L2 showed a steeper posterior inclination than both in thoracic scoliosis and controls. Also, L3 and L4 were significantly more posteriorly inclined in lumbar than in thoracic scoliosis, but not significantly more than in controls (Table 5, Figure 4 and 5).

Table 5. Significance of *post hoc* tests is shown for vertebral inclination of each spinal level between C7 and L5. n.a. =not applicable, based on insignificant MANOVA for that specific parameter. n.s. =not significant *post hoc* test. The significance level was set at <0.05.

Parameter		Thoracic scoliosis *versus* Lumbar scoliosis	Thoracic scoliosis *versus* controls	Lumbar scoliosis *versus* controls
		P	*P*	*P*
Vertebral inclination	**C7**	<0.001	0.002	n.s.
	T1	<0.001	<0.001	0.038
	T2	<0.001	<0.001	0.026
	T3	<0.001	<0.001	0.031
	T4	<0.001	<0.001	n.s.
	T5	<0.001	<0.001	n.s.
	T6	<0.001	<0.001	n.s.
	T7	<0.001	<0.001	n.s.
	T8	0.015	0.007	n.s.
	T9	n.a.	n.a.	n.a.
	T10	n.a.	n.a.	n.a.
	T11	n.a.	n.a.	n.a.
	T12	<0.001	n.s.	0.001
	L1	<0.001	n.s.	0.001
	L2	<0.001	n.s.	0.008
	L3	0.004	n.s.	n.s.
	L4	0.022	n.s.	n.s.
	L5	n.a.	n.a.	n.a.

Other research groups have also investigated the role of sagittal alignment of the scoliotic spine in relation to the coronal curve type. They also observed decreased kyphosis in thoracic scoliosis compared to idiopathic scoliosis of the lumbar type.[116, 146, 177] However, as was already noted by Voutsinas and MacEwen, measurement of kyphosis and lordosis lack significance for understanding the true shape of the spine and how it is mechanically loaded.[115] Grivas et al. found no differences in sagittal spinal alignment between mild thoracic, thoracolumbar and lumbar scoliosis. Their different outcomes can be attributed to the fact that, unlike in our study, they used a slightly different method in a smaller group of patients.

Upasani et al. observed greater pelvic incidence in AIS patients (regardless of curve type), while in the studies of Mac-Thiong et al., Yong et al. and in our study no differences in pelvic parameters were found between scoliotics and controls.[146, 177, 178] No differences in the morphology (pelvic incidence) and orientation (pelvic tilt and sacral slope) of the pelvis were observed between the cohorts in the present study.

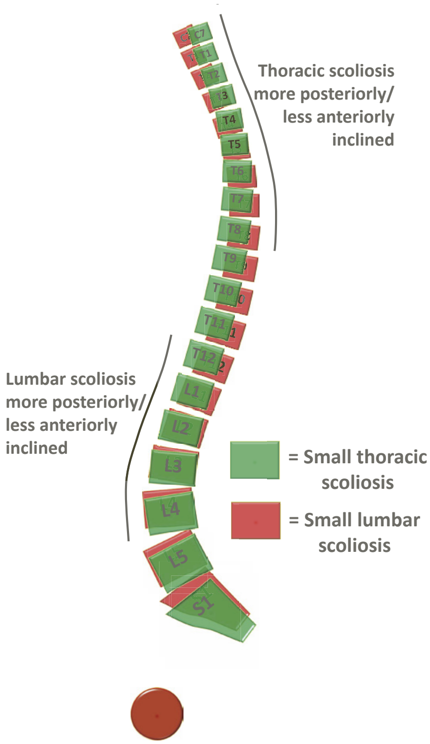

Figure 5. An overlay of the sagittal spino-pelvic alignment of thoracic scoliosis is shown on top of lumbar scoliosis. The hip-axis was set as the origin. Lines indicate the segments at which vertebral inclination was significantly different.

CONCLUSION

This study demonstrates that the sagittal profile of thoracic idiopathic scoliosis differs significantly from lumbar scoliosis already at an early stage of the condition. Furthermore, both curve types differ from the sagittal alignment of controls, although in different aspects. The fact that only posteriorly inclined vertebrae take part in the development of different scoliotic curve patterns, as was demonstrated in this study, is in accordance with earlier reported findings related to the rotational instability of the human spine and its role in the pathogenesis of scoliosis.

Chapter 8

The True Three-Dimensional Deformity of the Spine in Adolescent Idiopathic Scoliosis

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ABSTRACT

Background context. Although much attention has been given to the 3-D aspect of AIS in recent years, the true 3-D morphology of the different areas of the scoliotic spine has not been described in detail.

Purpose. To accurately define the three-dimensional (3-D) morphology of adolescent idiopathic scoliosis (AIS) as compared to normal anatomy.

Study design/setting. Cross-sectional study.

Patient sample. 77 AIS patient with computed tomographic scans of the spine, acquired for navigation purposes, were included. Non-idiopathic curves were excluded. Twenty-two controls were used as reference for normal anatomy. Of all subjects, standard upright PA and supine bending radiographs and MRI of the spine were available.

Outcome Measures. Coronal deviation, axial rotation and the exact length discrepancies in the reconstructed sagittal plane as defined per vertebra and disc, were analyzed for each curve and for the junctional segments.

Methods. True transverse sections of each vertebra and disc were reconstructed, taking inter- as well as intra-vertebral rotation and coronal and sagittal tilt into account. Using semi-automatic software, 'endplate-vectors' were calculated and complete 3-D spine reconstructions were acquired. Intraclass correlation coefficients for interobserver reliability were 0.98-1.00. This study was supported by a local institutional grant.

Results. All thoracic and (thoraco)lumbar, structural as well as nonstructural curves were *longer* anteriorly than posteriorly as measured from upper Cobb end vertebra to lower Cobb end vertebra (+3.8% and +9.4%, respectively), while the proximal and distal junctional segments were straight. The same thoracic segments in the controls showed the opposite, they were *shorter* anteriorly (–4.1%; $P<0.001$). In controls, lumbar segments were also longer anteriorly, but the anterior length was greater in scoliotics. Linear relations were observed between the standard upright radiographic Cobb angle, axial rotation and anterior-posterior length discrepancy as measured on the CT scans in all curves (thoracic $r>0.729$; $P<0.001$, (thoraco)lumbar $r>0.485$; $P<0.001$). Lateral radiographs had no value for prediction of the true 3-D morphology.

Conclusions. AIS consists of rotated, lordotic curves and straight junctional segments. Additional anterior length of the spine in scoliosis appears to be regional rather than global. This study is the first to elucidate the true patho-anatomy of scoliosis per region of the spine.

INTRODUCTION

The fact that idiopathic scoliosis is a complex three-dimensional (3-D) deformity of the spine rather than a simple lateral curvature has been well appreciated for a long time.[1] However, to the best of our knowledge, ours is the first study to describe the exact 3-D regional morphology of the individual curves and junctional segments in different types of AIS as compared to normal anatomy, using high-resolution computed tomography (CT) scans.

MATERIALS AND METHODS

Study population

The study was approved by our institutional ethics boards. All adolescents and young adults between 10 and 25 years of age diagnosed with adolescent idiopathic scoliosis who were planned to undergo spinal fusion after one institution started CT guided pedicle screw placement in July 2009, were included. Clinical charts, plain standing and supine bending radiograms as well as full-spine MRI were reviewed of all patients for in- and exclusion. Patients with congenital or neuromuscular scoliosis, or any other pathology of the spine, previous spinal surgery, neurological symptoms, syringomyelia, Chiari malformation, syndromes associated with growth abnormalities or incomplete work-up were excluded. Patients with left thoracic or right lumbar curves were excluded as well. CT scans in prone position (slice thickness 0.625mm, 64 Slice Multi-detector CT scanner, GE Healthcare, Chalfont, United Kingdom) had been obtained pre-operatively of all patients for navigation purposes. Curves were classified according to Lenke's classification system.[41] Twenty-two matched healthy controls were selected randomly from an existing database of patients who had undergone CT examination for trauma screening. The same in- and exclusion criteria were applied.

CT measurement method

Analysis software (ScoliosisAnalysis, Image Sciences Institute, Utrecht, the Netherlands) was developed using MeVisLab (MeVis Medical Solutions AG, Bremen, Germany) to reconstruct the coronal Cobb angle on the CT scan, axial rotation and the exact anterior-posterior length discrepancy of the curves as well as the proximal and distal junctional segments, semi-automatically. Measurements were performed by two trained observers. For assessment of variability between observers, they independently analyzed a subset of 10 randomly selected CT scans at separate sittings. Intraclass correlation coefficients (ICC) for all 3-D parameters were calculated to assess the inter-observer variability.

In the coronal plane, Cobb angles of the thoracic and lumbar curvature were measured in the standard manner on the most representative coronal CT image (Figure 1a).[39] For the measurement of axial rotation and the exact anterior-posterior length discrepancy of the curvatures, first, the 3-D position and orientation of all superior and inferior endplates between spinal levels T1 and the sacral endplate was determined. This enabled

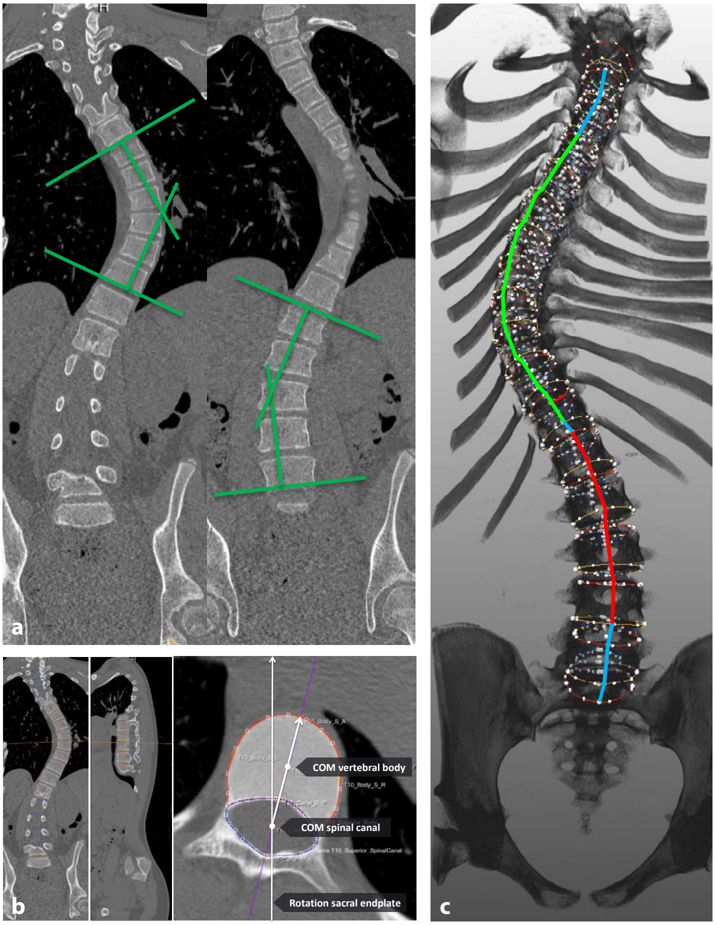

Figure 1. *a* Cobb angle measurements for coronal deviation of the main thoracic and (thoraco)lumbar curve was performed on the coronal slice on which the curve was best visible. *b* Axial rotation was measured for each individual endplate between T1 and L5 after delineation of the endplates in the coronal and sagittal plane. Anterior-posterior axis of the endplate was automatically found as the line throught the center of mass (COM) of the spinal canal segmentation and COM of the endplate segmentation. Axial rotation was defined as the angle between the anterior-posterior axis of the endplate and the anterior-posterior axis of the sacral plate in the horizontal plane. *c* Based on the anterior-posterior axis, the coordinates of the most anterior and most posterior part of each endplate was found. Sagittal anterior-posterior length difference was measured for all main thoracic and (thoraco)lumbar curves. In figure 1c the total anterior length of the main thoracic curve and (thoraco)lumbar curve are illustrated in *green* and *red*, respectively.

automatic reconstruction of the 'true' transverse section of each endplate (thickness 0.3mm), adjusting for vertebral displacement in all three planes. On these sections, the endplate and spinal canal were segmented manually and the anterior-posterior axis of each individual endplate was automatically found, using an image processing technique previously validated by Kouwenhoven et al.[25] Axial rotation per endplate was defined as the angle between each anterior-posterior endplate axis and the anterior-posterior axis of the sacral plate, since S1 is never part of the rotational deformity in idiopathic scoliosis (Figure 1b). Rotation to the right was assigned a positive value, rotation to the left a negative.

Based on the longitudinal axis and segmentations of the endplate, the coordinates of the exact anterior and posterior side of each superior and inferior endplate, and the anterior and posterior height of each vertebra and disc were determined automatically. The sum of the anterior and posterior heights of each vertebra and disc was calculated per curvature between the upper and lower Cobb end vertebra of each curve, and for the apical zones and junctional segments separately (Figure 1c). The distal junctional segment was represented by the lower end vertebra of the thoracic curve, one vertebra below and the disc in-between, and the proximal junctional segment as the upper end vertebra, one level above and the disc in-between. The apical region was defined as the apical vertebra and the two adjacent vertebrae and discs. 3-D morphology was compared with the normal anatomy in the controls. In addition, 3-D morphology was compared between different regions of the spine, the curves *versus* the proximal and distal junctional segments, and between different curve patterns (primary thoracic (Lenke I and II), primary (thoraco)lumbar (Lenke V) *versus* double/triple curve patterns (Lenke III, IV and VI)). Due to limited field of view, 3-D morphology of the upper thoracic curves down to T4 could not be accurately analysed in this study. To be able to compare the anterior-posterior length discrepancy for all subjects and spinal regions, relative anterior-posterior length differences (Δ(A-P)) were calculated, Δ(A-P) = (anterior length − posterior length) / posterior length × 100%. Positive values indicate a longer anterior than posterior column, while negative values indicate a longer posterior spinal column. Δ(A-P) was also calculated separately for the vertebral body and the disc. At last, we evaluated the relationship between the 3-D parameters from prone CT images with conventional parameters on the pre-operative standing radiographs (Cobb angles, thoracic kyphosis (T4–T12), lumbar lordosis (L1–S1) and Cobb angle correction on the bending radiographs).[39]

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS, Inc., Chicago, IL, United States). Mean and standard deviations (SD) were calculated for all continuous parameters. Kolmogorov-Smirnov tests were used to test for normality of distribution. For comparisons between AIS and controls, and between different curve patterns, independent samples t-tests and one-way ANOVA were used, respectively. Bonferroni's correction was applied for *post hoc* analyses. For comparisons between different regions, paired samples t-tests were used. For potential correlations, a scatterplot was produced and Pearson's correlation coefficient (r) was calculated. For significant, relevant correlations ($P<0.05$, $r>0.50$), ANOVA and the sum of squares was used to test for linearity and linear equations were extracted. The significance level was set at 0.05.

RESULTS

Demographics

Eighty-eight CT scans were initially available. Four patients were excluded because they had a congenital scoliosis, one had undergone previous spinal surgery, one patient had a syrinx on the pre-operative MRI scan and another patient had Marfan's disease. In addition, three patients had left thoracic curves and one case had incomplete pre-operative workup. Characteristics of the 77 included AIS subjects and 22 controls are shown in table 1.

Table 1. Demographic data are shown for the adolescent idiopathic scoliosis (AIS) cohort and matched controls. SD = standard deviation.

	AIS (n=77)	**Controls (n=22)**
Mean age ± SD	17.0±2.8	17.0±0.7
Girls, n (%)	60 (78%)	16 (73%)
Triradiate cartilage closed	77 (100)	
Risser's sign positive	77 (100)	
Thoracic curve pattern	53 (69%)	
Lenke I	37 (48%)	
Lenke II	16 (21%)	
(Thoraco)lumbar curve pattern	6 (8%)	
Lenke V	6 (8%)	
Double curve pattern	18 (23%)	
Lenke III	7 (9%)	
Lenke IV	2 (3%)	
Lenke VI	9 (12%)	

3-D morphology of the spine in AIS as compared to controls

As measured on the CT scans of the AIS patients, the thoracic curves had on average a Cobb angle of 58±11°, 24±9° right-sided axial rotation and were 3.8±2.8% longer anteriorly, reflecting true thoracic lordosis (table 2). In the controls, there was no lateral deviation, 1±3° pre-existent right-sided rotation (*P*<0.001) and the thoracic spine of the controls were longer posteriorly, reflecting normal thoracic kyphosis (–4.1±1.8%; *P*<0.001). So, thoracic AIS curves were on average 7.9% longer anteriorly over the same segments than the controls. Also without the discs, thus only the bony vertebral bodies, the thoracic curves were longer anteriorly (+2.6±3.1%), while in controls the same bony vertebrae were shorter anteriorly (–3.6±1.6%; *P*<0.001). The lumbar AIS curves had a coronal Cobb angle of 37±16°, 9±9° left-sided axial rotation and were 9.4±2.5% longer anteriorly. The lumbar spines of controls were 7.8±3.6% longer anteriorly, reflecting normal lumbar lordosis that is apparently increased in scoliosis (*P*<0.021). So, lumbar AIS curves showed 1.6% more anterior length compared to the lumbar spine of controls.

Table 2. Differences in three-dimensional outcome parameters are shown for the adolescent idiopathic scoliosis (AIS) cohort and matched controls. Δ(A-P) = anterior-posterior length discrepancy; n.a. = not applicable; n.s. = not significant.

	AIS (n=77)	**Controls (n=22)**	***P***
Thoracic curve parameters:			
Coronal Cobb (°)	58 ± 14	n.a.	n.a.
Axial rotation (°)	24 ± 9	1 ± 3	<0.001
Δ(A-P) (%)	3.8 ± 2.8	- 4.1 ± 1.8	<0.001
Δ(A-P), bone (%)	2.6 ± 3.1	- 3.6 ± 1.6	<0.001
(Thoraco)lumbar curve parameters:			
Coronal Cobb (°)	37 ± 16	n.a.	n.a.
Axial rotation (°)	- 9 ± 9	- 1 ± 5	0.001
Δ(A-P) (%)	9.4 ± 2.5	7.8 ± 3.6	0.021
Δ(A-P), bone (%)	3.0 ± 3.2	3.9 ± 3.8	n.s.

3-D morphology of different spinal regions

In the comparison of different spinal regions, most anterior-posterior length discrepency as well as rotation was observed in the apical regions of all curves (table 3). In contrast, in the proximal and distal junctional segments between the curves, no clear anterior-posterior length discrepancy and no rotation was observed (*P*<0.001).

Table 3. Differences in anterior-posterior length discrepancy and axial rotation are shown for different regions of the spine in seventy-seven subjects with adolescent idiopathic scoliosis (n=77). Δ(A-P) = anterior-posterior length discrepancy.

	Proximal Junctional segment	Apical zone thoracic curve	Distal Junctional segment	Apical zone (thoraco)lumbar curve	*P*
Δ(A-P) (%)	–1.3 ± 4.7	7.1 ± 4.8	1.0 ± 2.7	11.2 ± 4.1	<0.001
Axial rotation (°)	5 ± 9	24 ± 9	- 1 ± 11	- 9 ± 9	<0.001

Morphology of different AIS patterns

In all curve patterns (Lenke 1-6), structural as well as nonstructural, primary as well as compensatory, the anterior length exceeded the posterior length of the curve from Cobb to Cobb (table 4).

Table 4. Differences in three-dimensional outcome parameters are shown for adolescent idiopathic scoliosis subjects with three different curve types. MT = main thoracic; (T)L = (thoraco)lumbar curve; Δ(A-P) = anterior-posterior length discrepancy; n.s. = not significant.

	Thoracic curve pattern (n=53)	(Thoraco)lumbar curve pattern (n=6)	Double curve pattern (n=18)	*P*
Thoracic curve parameters:				
Structural/non-structural	*Structural*	*Non-structural*	*Structural*	
Coronal Cobb (°)	60 ± 11	40 ± 13*	61 ± 17	0.001
Axial rotation (°)	26 ± 7	14 ± 6*	24 ± 12	0.004
Δ(A-P) (%)	4.2 ±2.7	1.8 ± 2.2	3.6 ± 3.1	n.s.
(Thoraco)lumbar curve parameters:				
Structural/non-structural	*Non-structural*	*Structural*	*Structural*	
Coronal Cobb (°)	28 ± 10*	57 ± 12	55 ± 12	<0.001
Axial rotation (°)	- 4 ± 5*	- 20 ± 6	- 19 ± 8	<0.001
Δ(A-P) (%)	8.6 ± 2.2*	10.8 ± 2.3	11.4 ± 2.2	0.001

**P*<0.05 in *post hoc* analysis

Coupling between the three-dimensional changes

Pearson's correlation analysis revealed for the thoracic curves an excellent correlation between the coronal reconstructed Cobb angle *versus* axial rotation as well as *versus* ΔA-P (r=0.806, P<0.001 and r=0.729, P<0.001, respectively). Rotation and ΔA-P also correlated significantly with each other (r=0.748, P<0.001).

Correlation of radiographic parameters with 3-D morphology

Cobb angle as measured on prone CT scans and Cobb angles on standing radiographs correlated significantly and were linearly related (thoracic: r=0.933, P<0.001 and (tho-

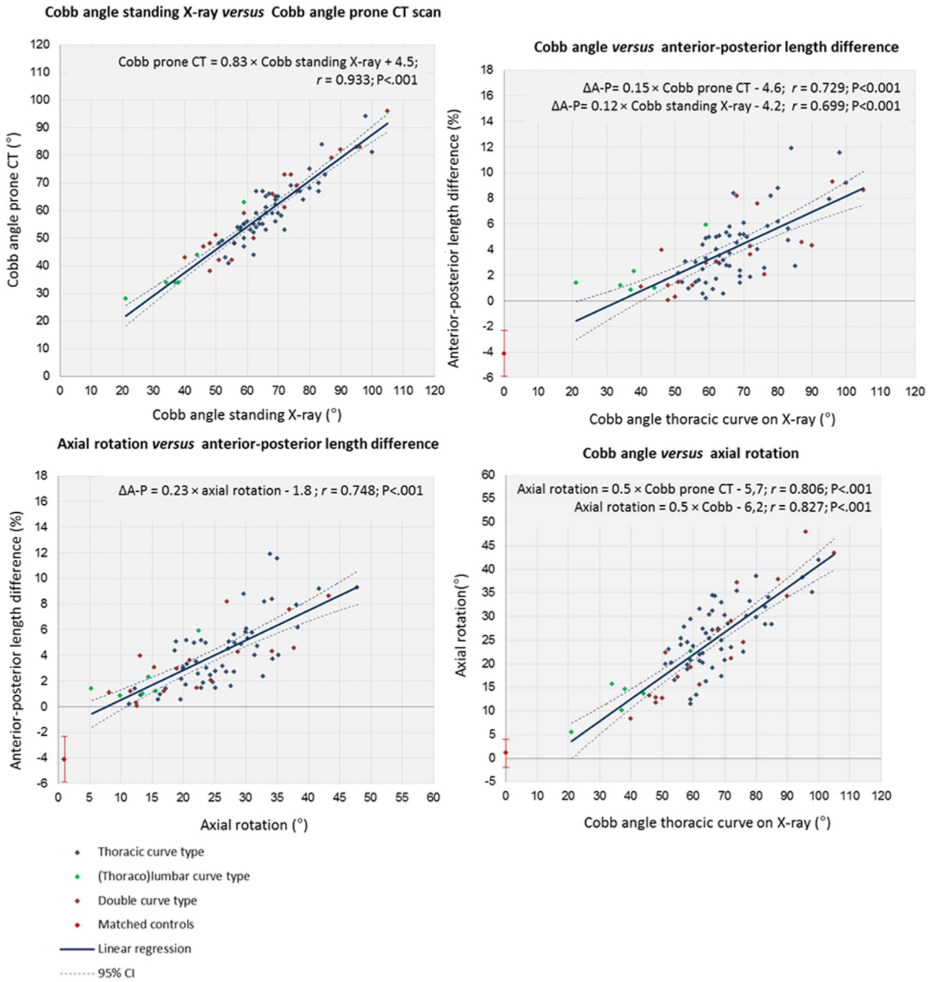

Figure 2. *a.* Correlation between Cobb angle of the thoracic curve on standing AP radiographs *versus* prone CT scans. *b.* Correlation between the standing Cobb angle and axial deformity. *c.* Cobb angle *versus* sagittal deformity (*figure 2c*). *d.* Correlation of the axial and sagittal deformity (*figure 2d*). Pearson's correlation coefficient *r*, linear regression equation, line and significance are shown including the 95% confidence interval (95% CI). For the control cohort, mean and standard deviations (error bars) are shown.

raco)lumbar: r=0.959, P<0.001; figure 2a). Additionally, significant correlations and linear relations were also observed between Cobb angle measurements on the standing radiograph and axial rotation and Δ(A-P) on the CT scans (P<0.001; figure 2b-d). Scatterplots and equations in figure 2 demonstrate the linear relations between the Cobb angle on standing radiographs and the prone, CT derived Cobb angle, axial rotation and the anterior-posterior length discrepancy on CT scans. For practical purposes, with every 10° increase in Cobb angle of the thoracic curve on the standing radiograph, axial

Table 5. Pearson's correlation coefficients are shown for all significant correlations between measurements on two-dimensional (2-D) radiographs and three-dimensional (3-D) computed tomographic measurements of the same curvature. The statistical significance level was set at 0.05. MT = main thoracic; (T) L = (thoraco)lumbar curve; Δ(A-P) = anterior-posterior length discrepancy; n.s. = not significant. *P<0.05; **P<0.001

3-D Computed tomography / *2-D Conventional radiography*	*Anterior-posterior radiograph*	*Lateral radiograph*		*Lateral bending radiograph*
	Cobb angle	Thoracic kyphosis	Lumbar lordosis	Cobb angle correction
Thoracic curve parameters:				
Coronal Cobb	0.933**	n.s.	n.s.	- 0.404**
Axial rotation	0.827**	n.s.	n.s.	- 0.323*
Δ(A-P)	0.699**	n.s.	n.s.	- 0.277*
(Thoraco)lumbar curve parameters:				
Coronal Cobb	0.959**	n.s.	n.s.	- 0.761**
Axial rotation	0.843**	n.s.	n.s.	- 0.713**
Δ(A-P)	0.459**	n.s.	n.s.	- 0.452**

rotation increased 5° and the relative anterior length of the curve increased 1.2%. No significant correlations were observed between measurements of thoracic kyphosis and lumbar lordosis on the standing lateral radiograph and 3-D parameters. Moreover, correction on lateral bending radiographs correlated significantly with the morphologic CT parameters in all three dimensions (P<0.05; table 5).

Reliability of measurements

ICC's for inter-observer measurements reliability were 0.98 (95%CI: 0.97-0.99) for Cobb angle, 0.99 (0.99-1.00) for axial rotation and 0.97 (0.92-0.98) for the anterior-posterior length discrepancy calculations.

DISCUSSION

Idiopathic scoliosis typically consists of three curves of varying severity and structurality. Our CT study is, to the best of our knowledge, the first to provide an accurate and detailed quantitative description of the *in vivo* 3-D morphology of AIS per separate region of the spine. 3-D CT reconstructions are the 'gold standard' for quantitative assessment of the morphology of *in vivo* structures.[180] Drawback is that they are not obtained in a standing position, for that reason we correlated CT measurements to standard upright radiography measurements.

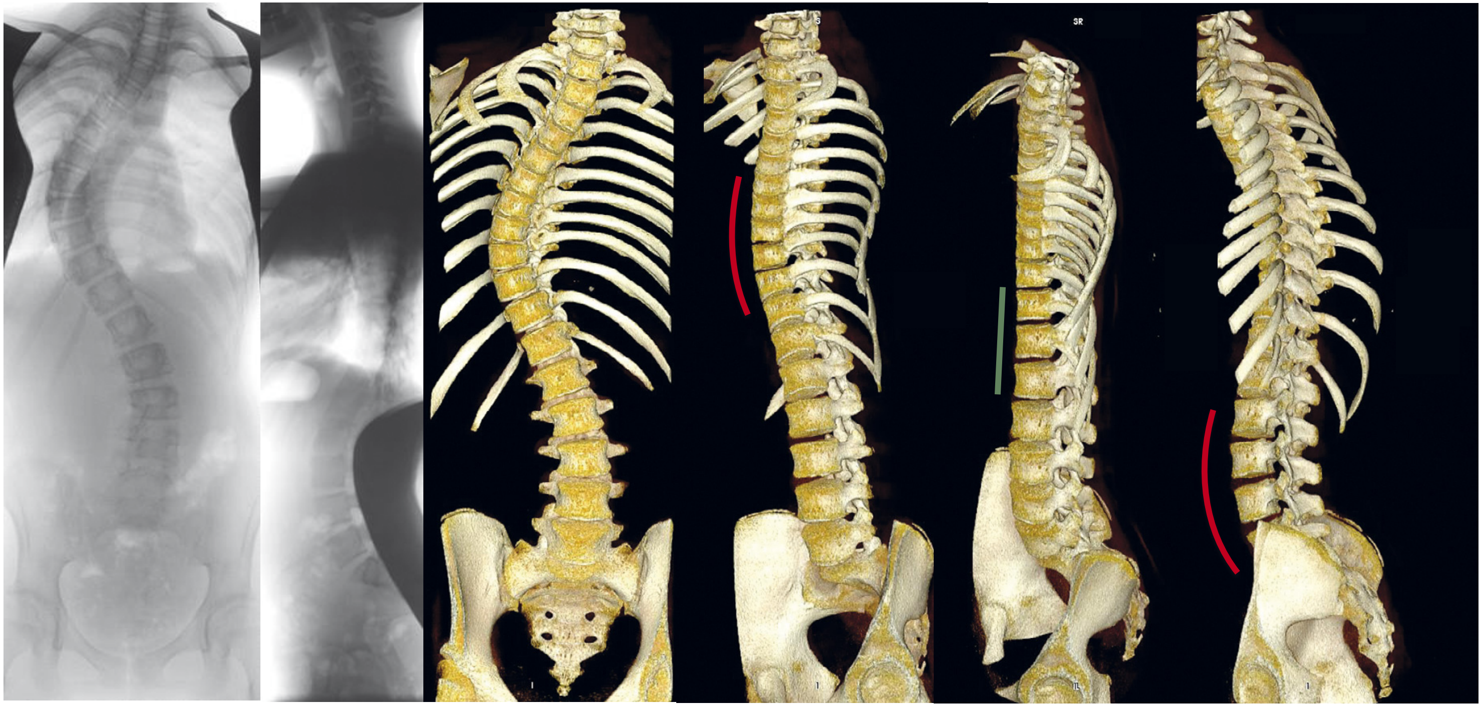

Figure 3. Antero-posterior and lateral radiographs, and computed tomography reconstructions (OsiriX 64-bit; OsiriX Foundation, Los Angeles, CA, USA) are shown from an anterior and anterolateral view. In this representative 15-year-old patient with adolescent idiopathic scoliosis with a typical thoracic curve pattern, anterior overgrowth cannot be observed on the lateral radiography. The rotated lordoses of both thoracic and the (thoraco)lumbar curvatures, with a clearly longer anterior spinal column than posterior elements, are shown in *red*, and the straight junctional segment in-between in *green* from a true lateral view for these regions.

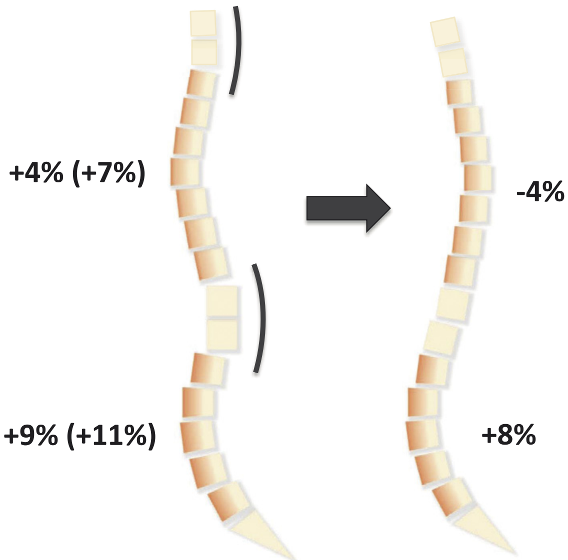

Figure 4. If derotation of the apical lordoses back to the midline is performed without complete restoration to normal kyphosis, errors, such as junctional kyphosis, might occur in the sagittal plane. Percentages indicate the mean anterior overgrowth in the scoliotic curves and apices, and in the same segments in the normal spine.

In the coronal plane, we found an excellent correlation between the standard upright radiographic Cobb measurement on the one hand, and the reconstructed Cobb angles from the prone CT on the other hand. The CT derived Cobb showed some underestimation of the curve magnitude dependent of curve severity. All AIS curves, structural as well as nonstructural, showed from upper to lower Cobb end vertebra greater anterior than posterior length. For the thoracic spine this is opposite to normal kyphotic anatomy: in thoracic curves the anterior aspect of the thoracic spine was on average 7.9% longer compared to controls (figure 4). The nonscoliotic lumbar spine obviously is already in lordosis, but relative anterior length of a lumbar or thoracolumbar curve was also greater than in normals by an average of 1.6%. The apical zones in the curvatures contribute most to this observed length discrepancy. The proximal and distal junctional segments, on the other hand, were straight with a non-significant tendency of the proximal junction to be in slight kyphosis (figure 3).

The changes in the coronal, axial and sagittal plane showed a linear relationship, these are therefore coupled phenomena. This implies that:

1. 3-D development of scoliosis follows a rather uniform and predictable pattern; with increasing deformity in one plane, the other two planes follow simultaneously.[181]

2. Cobb angles on the standing radiograph are indicative of the 3-D morphology of the curve, severe curves not only had higher Cobb angles, but were also characterized by more axial rotation and anterior lengthening than smaller curves (Figure 2 a-d). The relationship between coronal Cobb angle and anterior lengthening can be expressed by the formula: Δ(A-P)MT = 0.12 $\times$ CobbMT − 4.2. With every 10 degrees of increase in Cobb angle, rotation increases by an average of 5° and the relative anterior length of the curve increases 1.2%.
3. These findings hold true for all curve types, both structural and nonstructural ones.

Positioning may have influenced our results, since scans in scoliosis were taken in a prone position whereas the control scans were taken in a supine position. This may have affected the 3-D morphology of the discs. Sub-analyses on the individual bony vertebrae, which are not position dependent, however, showed that the anterior length of the curvatures was still significantly greater than posteriorly, while in controls the anterior length of the same bony segments was smaller. Furthermore, there was a strong relationship between CT derived measurements and the standard upright parameters. Therefore, we believe that our findings in general hold true.

Plain radiography severely obscures the true complex configuration of the spine in scoliosis. The always existent apical lordosis is, due to its rotated and deviated orientation, not readily visible on conventional lateral radiographs.[37, 182, 183] This issue is further complicated by terminology: The spine between the vertebrae T4 and T12 in scoliosis can show a more or less kyphotic angle whereas the intervening vertebrae are without exception in segmental rotated lordosis (Figure 3). This has also been referred to by a number of authors in the previous century.[34, 35, 37] Recently, Hayashi et al. came to a similar conclusion in a study on spinal reconstructions of biplanar radiographs.[183] In most studies a wide variety of sagittal alignments of the scoliotic thoracic spine, from lordosis to thoracic hyperkyphosis, is observed and no strong correlation with the severity of the deformity in the coronal plane has been found.[129, 178, 184] Stagnara introduced *le plan d'élection*, a rotated view that projects the maximal AP, or sagittal curvature of the spine.[36] Using this sagittal Stagnara view, Dickson et al. observed in 70 AIS patients that 75% of the curves were lordotic, 24% were straight and 1% kyphotic. In contrast, on their standard lateral radiographs the overall thoracic kyphosis was 20 degrees. Even in the so called sagittally straight spines, the apical vertebrae were wedged, with greater anterior height than posteriorly.[37]

All scoliotic vertebrae and, due to intrinsic torsion of vertebrae and discs, all endplates of scoliotic vertebrae are axially rotated, laterally deviated and tilted in a different way, also within one vertebra, than the adjacent ones. Therefore, we used 'endplates-vectors', instead of 'vertebra vectors' as used in biplanar radiography 3-D reconstructions.[185] The 'true' sagittal profile of the curvatures and junctional zones of the spine was calculated using these endplate vectors as reference for determining the true anterior and posterior aspect per vertebra, taking inter-vertebral torsion, inter-vertebral rotation as well as sagittal and coronal tilting of each individual endplate into account.

This is not the first morphometric investigation in which the anterior-posterior length discrepancy of AIS curvatures was studied in detail and compared to normal anatomy. Porter reported on differences in total axial length of the vertebral bodies and spinal canal in skeletons of scoliotic patients and normals. He observed relatively shorter spinal canals in the scoliotic spines and found a relation of the length discrepancy with the severity of the curves.[56, 186] In Porter's study, the rotation of the vertebral bodies was taken into account, but the anterior-posterior length difference of the spinal column (vertebral bodies and intervertebral discs) was measured for the complete thoracic and lumbar spine. More recently, Chu et al. and Guo et al. reported shorter spinal canals, decreased interpedicular distance and a relatively longer anterior spinal column on reformatted magnetic resonance images of AIS patients compared to controls.[57, 187]

Our study demonstrates the consequences for corrective surgery strategies: The greater anterior length, especially around the apex, precludes true derotation as well as true and harmonious restoration of normal thoracic kyphosis unless either aggressive posterior lengthening or anterior shortening is employed. Otherwise, either rotation will persist, or the pre-existent thoracic lordosis will be rotated into the sagittal plane, causing potential junctional problems. We observed a trend towards kyphosis for the proximal junctional segment, while the distal junctional segment was more or less straight. This may explain why proximal junctional kyphosis is reported more frequently (8-46%) than distal junctional problems (7-15%).[188-193]

Stiffness implies certain tissue characteristics that prevent deformation, whereas, in idiopathic scoliosis, coronal plane flexibility apparently depends more on the true 3-D anatomy. Curves with greater anterior length showed less correction on the bending radiographs, due to the anatomical impossibility to reduce the access length of the anterior column into the midline.

What constitutes the initiating event in AIS remains largely unknown. Different investigators have postulated the hypothesis that lordosis, active anterior overgrowth of the vertebrae or posterior tethering of the spinal cord, may cause AIS.[56, 57, 186, 187] We found that anterior length was most pronounced around the apex, whereas between the curves there was no anterior-posterior asymmetry. Thus, anterior 'overgrowth' apparently is regional rather than general. The fact that compensatory curves follow the same pattern as primary curves, and that this excess of anterior length is mainly localized in the discs, indicates that it may be a secondary phenomenon rather than an active growth process. If rotation around a posterior axis is the initiating event, as has been suggested by others, this will unload the anterior column from compressive forces, allowing the discs to expand passively and the anterior vertebral bodies to grow according to Hueter Volkmann's law.[5, 28, 172, 173]

CONCLUSION

All AIS curve types follow a rather standard and pre-determined evolution in all three planes, where increased rotation is associated with increasing Cobb angle and increased anterior length. Cobb angle measurement on conventional standing coronal plane radiographs can be used to estimate true 3-D morphology. Our findings are relevant both theoretically and practically. First, they better define the true regional nature of scoliosis and differentiate between different areas in the scoliotic spine. Furthermore, for scoliosis surgeons, the technical difficulties that are encountered in obtaining true harmonious 3-D realignment are explained.

Chapter 9

Three-Dimensional Characterization of Torsion and Asymmetry of the Intervertebral Discs versus Vertebral Bodies in Adolescent Idiopathic Scoliosis

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ABSTRACT

Study Design. Cross-sectional study.

Objective. To compare the relative contribution of the vertebral bodies and intervertebral discs to the three-dimensional spinal deformity in adolescent idiopathic scoliosis.

Summary of Background Data. There is an ongoing discussion about the causal role of skeletal growth processes in the etio-pathogenesis of adolescent idiopathic scoliosis. Contradictory findings have been reported on the individual contribution of the vertebral bodies as compared to the discs to the coronal deformity. As far as we know, the true three-dimensional deformity of the discs and vertebral bodies have not yet been described.

Methods. High-resolution computed tomographic scans of seventy-seven patients with severe adolescent idiopathic scoliosis were included. Torsion and anterior-posterior and right-left asymmetry of each individual vertebral body and intervertebral disc was studied from T2 to L5, using semi-automatic analysis software. True transverse sections were reconstructed along the anterior-posterior and right-left axis of all endplates. These 'endplate-vectors' were calculated semi-automatically, taking rotation and tilt into account. Torsion was defined as the difference in axial rotation between two subsequent endplates. Asymmetry was defined as the relative anterior-posterior or right-left height difference of the discs and vertebrae.

Results. There was at least <u>three times</u> more torsion, anterior overgrowth and coronal wedging in the discs than in the vertebrae in the thoracic as well as in the (thoraco)lumbar curves (P<0.001). These values correlated significantly with the Cobb angle (r≥0.37; P<0.001). Anterior overgrowth and coronal asymmetry was greater in the apical regions whereas torsion was most pronounced in the transitional segments between the curves.

Conclusions. The discs contribute more to 3-D deformity than the bony structures, and there is significant regional variability. This suggests an adaptive rather than an active phenomenon.

INTRODUCTION

The morphological changes of the vertebral bodies and intervertebral discs (IVDs) in patients with progressive adolescent idiopathic scoliosis (AIS) have been investigated extensively to date. The difference in the amount of coronal plane deformity in the discs *versus* the vertebral bodies was in particular the target of many investigations focused on the pathogenesis of AIS.[194-203] On conventional two-dimensional radiographs, it was observed that the discs were more wedge-shaped than the vertebral bodies in mild scoliotic curves whereas the wedging of the discs and vertebrae became more or less equal in more severe scolioses.[195, 202] These findings suggest that AIS is primarily a deformation of the discs and that, according to Hueter-Volkmann's law, the deformation of the vertebral bodies is secondary.[172, 173, 204, 205] However, at the same time, others reported increased coronal wedge angles of the vertebral bodies already in mild AIS, indicating abnormal vertebral growth.[2, 198-201, 203]

As has been known for more than a century, AIS is a three dimensional (3-D) deformity of the spine, characterized by axial rotation, lateral deviation and segmental extension of the spine.[1, 206] Our study describes the 3-D deformation of the discs and vertebrae in AIS as accurately as possible by using a series of high-resolution computed tomography (CT) scans.

MATERIALS AND METHODS

Population

All AIS patients that were planned to undergo scoliosis surgery in one of our centers between June 2011 and May 2013 were enrolled in this study. All had undergone CT imaging as a preparation for navigated surgery. Clinical and radiological charts were reviewed for in- and exclusion. Inclusion criteria were: diagnosis of adolescent idiopathic scoliosis, complete pre-operative work-up consisting of anterior-posterior, lateral and bending radiographs, as well as screening for neural axis abnormalities using magnetic resonance imaging. Exclusion criteria were: other spinal pathology than idiopathic scoliosis, previous spinal surgery, neurological symptoms, neural axis abnormalities on MRI, syndromes associated with disorders of growth and left convex thoracic curves/right convex (thoraco)lumbar curves. Prior to surgery, CT-scans (slice thickness 0.625mm, in-plane resolution 0.352mm/pixel, 64 Slice Multi-detector CT scanner, GE Healthcare, Chalfont, St. Giles, United Kingdom) of the spine were obtained in prone position with the arms on the side, identical to the intra-operative positioning of the patients. Conventional anterior-posterior, lateral and bending radiographs were reviewed by one of the investigators to determine curve type according to the Lenke classification, Risser's sign, triradiate cartilage closure and end vertebrae, apical levels and Cobb angles of the curvatures.[39, 42, 122]

Computed tomographic measurements

Two trained observers used in-house developed software (ScoliosisAnalysis, Image Sciences Institute, Utrecht, Netherlands) to measure mechanical torsion, as well as the anterior-posterior and right-left asymmetry of each individual vertebra and disc between T2 and L5, semi-automatically.

The procedure consisted of the following seven steps (Figure 1): (I) The position and orientation of each superior and inferior endplate was defined by manually angulating a plane in the three orthogonal directions; (II) the end-plates where delineated in the angulated plane on which the endplate was best visible to reconstruct 'true' transverse sections of the endplates; (III) Using a technique that was previously validated by Kouwenhoven et al., the software automatically calculated the center of mass of the spinal canal, the center of mass of the endplate, the anterior-posterior axis of the endplate (a line between the center of mass of the endplate and spinal canal) and the right-left axis (the line perpendicular to the anterior-posterior axis).[25] (IV) The exact coordinates of the most anterior, posterior, left and right side of each endplate was calculated. Next, (V) torsion of each vertebra (intra-vertebral torsion) and disc (inter-vertebral torsion) was calculated. (VI) The exact distance between the coordinates of two adjacent endplates defined the anterior, posterior, left and right height of the vertebral bodies/discs. (VII) The final outcome parameters were calculated for the total main thoracic and (thoraco)

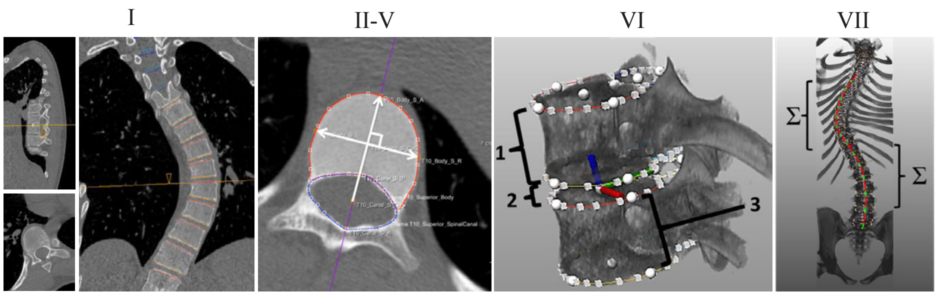

Figure 1. The image processing technique for semi-automatic analysis of the 3-D morphology of the vertebrae and intervertebral discs on high resolution computed tomography scans of adolescent idiopathic scoliosis patients consisted of six-steps as described in the methods section. After delineation of the orientation of the inferior and superior endplates in 3-D (I), true transverse sections of each individual endplate were reconstructed. Based on the center of mass of segmentations of the endplate and spinal canal, the anterior-posterior ('endplate-vectors') and right-left axes were calculated (II-IV). Using these vectors, mechanical torsion as well as anterior-posterior and right-left asymmetry (V) were computed for all intervertebral discs and vertebral bodies in the thoracic and (thoraco)lumbar curve (VI). 1=anterior vertebral body height, 2=anterior intervertebral disc height, 3=height of the left side of the vertebral body.

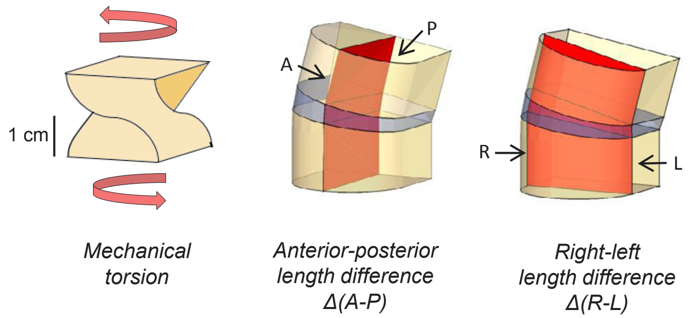

Figure 2. Schematic illustrations of the outcome parameters. Mechanical torsion was defined as degrees of axial rotation between the superior and inferior endplate, normalized for the height (°/cm). Anterior-posterior and left-right length differences were computed in the true sagittal and coronal plane. A,P,R,L indicate anterior, posterior, right and left vertebral body height.

lumbar curvature (including primary as well as compensatory curves) and for the apical and transitional regions of the spinal curvatures. The total curve was defined as all vertebrae/discs between the lower and upper end vertebra of the curve, identical to radiographic Cobb angle measurement. The apical region included the apical vertebra and the adjacent segment above and below (3 vertebral bodies or 2 discs) and the non-apical region all other vertebrae/discs between the end vertebrae. Because each patient has different length, each curvature includes a different number of vertebral bodies and discs, and the intervertebral discs have different size as compared to the vertebral bodies, all outcome parameters were normalized for height for comparison. The final outcome parameters (figure 2) consisted of:

- Torsion per centimeter height: This was defined as the angle between the anterior-posterior axis of the superior endplate and the anterior-posterior axis of the inferior one of the same vertebra or disc in the axial plane divided by the height in centimeters. For example, if we found three vertebrae with a total height of 6.0cm and a total torsion of 15°, torsion was 2.5°/cm.
- Anterior-posterior height difference (Δ(A-P)): The sum of the anterior height of the included vertebral bodies/discs relative to the sum of the posterior heights. Positive values indicated the percentage of greater anterior height compared to posterior height (kyphosis).
- Right-left height difference (Δ(R-L)): The sum of the lengths of the right side of the vertebrae/discs divided by the sum of the lengths of the left side.

Measurement accuracy and reliability

For intra- and interobserver reliability analysis of the different outcome parameters, the two observers independently analyzed a randomly selected subset of ten CT scans of the AIS subjects. In addition, the accuracy of the quantitative assessment of torsion and vertebral body/disc heights was evaluated on ten CT scans of adolescents without spinal pathology. From the analyses of mechanical torsion and right-left asymmetry on this set of normal, symmetrical spines followed that the error of our measurements of mechanical torsion and height of vertebral bodies and discs was 0.1°/cm and 0.2mm, respectively.

Statistical analysis

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Potential outliers were identified. Statistical analyses were performed in terms of intra- and interobserver variability, which were obtained as intraclass correlation coefficients (ICC). 3-D morphology of the vertebral bodies was compared to the discs using paired samples t-tests. A Bonferroni correction was applied for multiple testing, therefore, a P-value <0.002 was considered as statistically significant. Pearson's correlation coefficient (r) defined the relationship between torsion, coronal and sagittal asymmetry and Cobb angle. For significant correlations, linear regression analysis was performed.

RESULTS

Population

Eleven subjects were excluded (six had associated congenital or neuromuscular pathologies, one had undergone scoliosis surgery prior to the CT scan, one had incom-

Table 1. Characteristics are shown for all adolescent idiopathic scoliosis patients that were enrolled in this study. SD=standard deviation.

		n=77
Age (years)	Range	11-26
	Mean±SD	17.0±2.8
Girls, n (%)		60 (78%)
Lenke curve type		
I		37 (48%)
II		16 (21%)
III		7 (9%)
IV		2 (3%)
V		6 (8%)
VI		9 (12%)
Main Thoracic Cobb angle (°):	Range	28-96
	Mean±SD (°)	58.7±13.7
(Thoraco)lumbar Cobb angle (°):	Range (°)	11-79
	Mean±SD (°)	36.9±16.1

plete radiological charts and three had atypical left convex thoracic curves). A total of seventy-seven subjects were enrolled. They were on average 17.1±2.9 years of age and sixty (78%) were girls (demographics are shown in table 1). Seventy-one (92%) had a structural thoracic curve and twenty-six (34%) a structural (thoraco)lumbar curvature based on bending criteria.[41, 207] Ultimately, mechanical torsion and asymmetry were analyzed in a total of 1232 vertebrae en 1155 discs.

Mechanical torsion

In the thoracic curves, torsion was significantly greater in the IVDs when compared to the vertebral bodies (6.2±2.3 °/cm height *versus* 1.9±0.7°/cm, respectively; $P<0.001$). In the (thoraco)lumbar curves as well, torsion of the IVDs was greater compared to vertebral torsion: 4.1±2.6°/cm *versus* 1.2±0.4°/cm; $P<0.001$) (table 2). In the apical as well as transitional levels of the thoracic curves, significantly more torsion was found in the discs than in the vertebral bodies (apex, respectively 6.0±2.4°/cm *versus* 1.8±0.9°/cm; transitional region, 6.3±3.1°/cm *versus* 2.1±0.9°/cm; $P<0.001$; figure 3a). In addition, a trend was observed that torsion was more pronounced in the transitional levels than around the apex, however, this did not reach statistical significance. In the different regions of the (thoraco)lumbar curves, we also observed that the discs were significantly more affected by torsion compared to the vertebral bodies: apical region, 3.8±2.5°/cm torsion in the disc *versus* 0.9±0.4°/cm in the vertebrae; transitional region, 4.7±3.2°/cm *versus* 1.5±0.8°/cm, respectively ($P<0.001$). Again, a trend was observed that torsion was more pronounced in the transitional, non-apical levels of the curvature. In the (thoraco) lumbar curves, this trend became statistically significant ($P\leq0.001$).

Table 2. Three-dimensional morphology of the vertebral bodies and intervertebral discs in the thoracic and (thoraco)lumbar curves. Δ(A-P)=anterior-posterior length difference, Δ(R-L): right-left difference. For Δ(A-P) and Δ(R-L), positive values indicate greater anterior and right height, respectively.

		Vertebral bodies + discs	Vertebral bodies	Intervertebral discs	*P*-value
Thoracic curve	Torsion	2.8±0.8 °/cm	1.9±0.7 °/cm	6.2±2.3 °/cm	<0.001
	Δ(A-P)	+3.9±2.7 %	+2.6±3.1 %	+9.8±7.3 %	<0.001
	Δ(R-L)	+18.6±7.1 %	+13.5±6.6 %	+45.7±24.2 %	<0.001
(Thoraco)lumbar curve	Torsion	1.9 ±0.7 °/cm	1.2±0.4 °/cm	4.1±2.6 °/cm	<0.001
	Δ(A-P)	+9.4±2.7 %	+3.1±3.8 %	+ 34.8±20.7 %	<0.001
	Δ(R-L)	−11.5±6.0 %	−7.2±5.5 %	−24.1±11.4 %	<0.001

Anterior-posterior asymmetry

All thoracic and (thoraco)lumbar curves had greater anterior than posterior length. In the disc-vertebra comparison, the discs contributed most to the anterior overgrowth

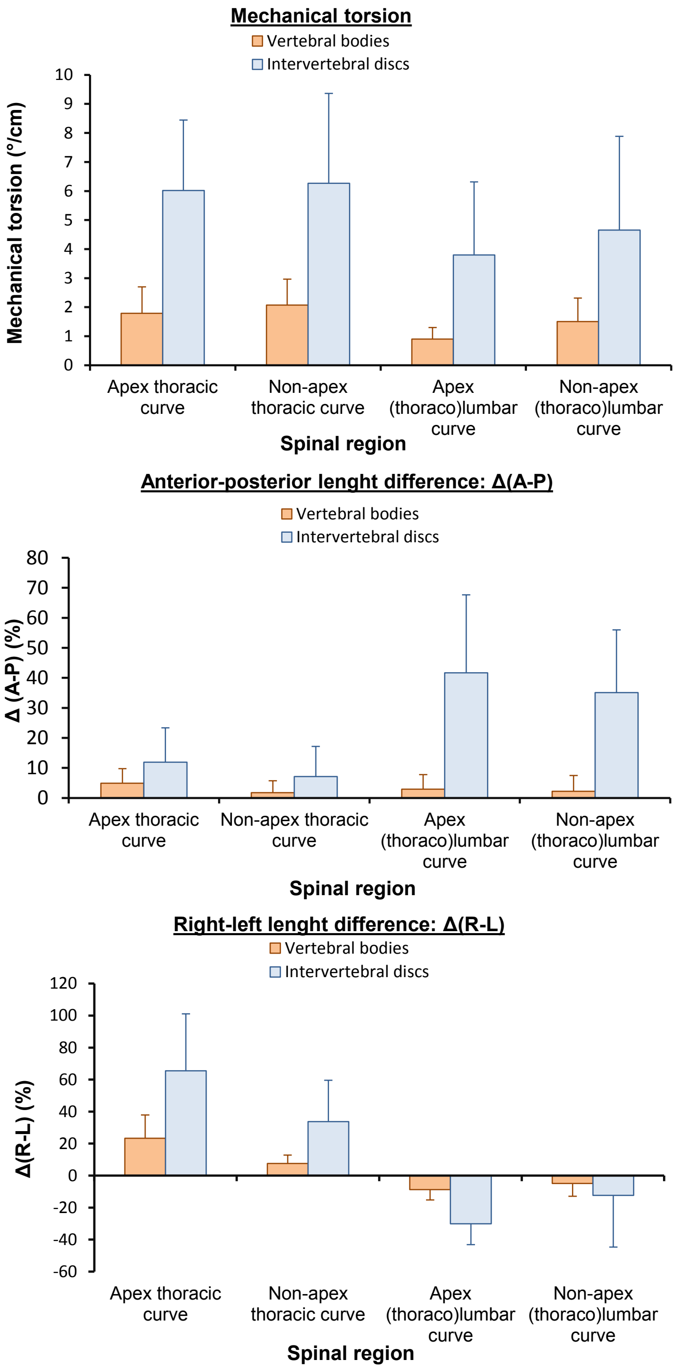

Figure 3: Three-dimensional morphology of the intervertebral discs and vertebral bodies in different regions of the spinal curvature. In all spinal regions, the differences between the discs and vertebrae were statistically significant (*P*<0.001).Error bars indicate standard deviations.

in the thoracic as well as the (thoraco)lumbar curves (table 2). The thoracic discs were significantly longer anteriorly compared to the vertebral bodies (+9.8±7.3% and +2.6±3.1%), especially around the apex (figure 3b). Differences in discal and vertebral asymmetry were statistically significant around the apex and in the transitional zone ($P<0.001$ and $P\leq0.007$, respectively). Also, in the (thoraco)lumbar spine a significant difference was observed between the discs (+34.8±20.7%) and vertebrae (+3.1±3.8%). In more detail, sagittal asymmetry of the discs was greatest around the apex ($P<0.001$) whereas asymmetry of the vertebrae was small in the apical as well as the non-apical region of the curve ($P>0.05$).

Right-left asymmetry

The right side of the thoracic curves was on average 18.6±7.1% longer than the left side and the right side of the (thoraco)lumbar curves was 11.5±6.0% shorter (table 2). Also in the coronal plane, the discs were significantly more wedge shaped than the vertebrae in the apical and non-apical regions of thoracic (45.7±24.2% *versus* 13.5±6.6%) and (thoraco)lumbar curves (–24.1±11.4% *versus* –7.2±5.5%; Figure 3c).

Relation with curve severity

Linear regression analysis showed a significant increase in torsion, anterior-posterior and right-left asymmetry with increasing Cobb angle in the thoracic and (thoraco) lumbar curvatures (thoracic, $r=0.37$, $r=0.70$ and $r=0.55$; (thoraco)lumbar, $r=0.66$, $r=0.46$, $r=-0.74$, respectively; $P\leq0.001$). No significant correlation was found between Cobb angle and relative contributions of the discs and vertebrae in terms of mechanical torsion and coronal and sagittal asymmetry, indicating that the discs contributed more to axial, sagittal and coronal deformity than the vertebrae, independent of the severity of the curves (figure 4a-f).

Reliability

ICCs for intra- and inter-observer reliabilities were 0.92 (95% confidence interval: 0.82 – 0.97) and 0.89 (0.74 – 0.95) for torsion, 0.99 (0.98 – 1.00) and 0.99 (0.98 – 1.00) for Δ(A-P) and 0.99 (0.99 – 1.00) and 0.99 (0.98 – 1.00) for Δ(R-L), respectively.

DISCUSSION

If the normal spinal curvature decompensates into a spinal deformity (for whatever reason), severe progression during the adolescent growth spurt can lead to a complex 3-D spinal and truncal deformity. Our study is, to the best of our knowledge, the first to accurately report on the relative contributions of the disc as compared to the vertebral

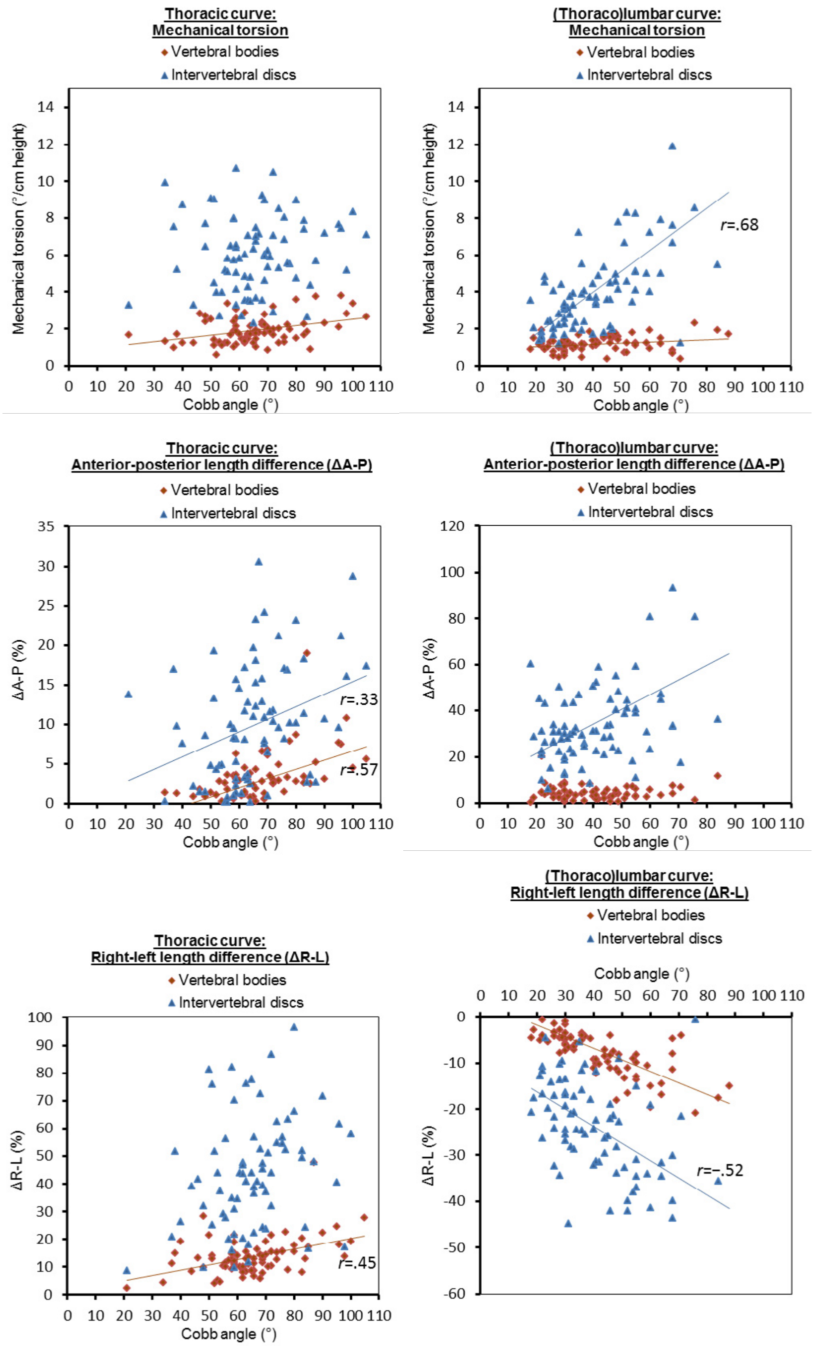

Figure 4. In these scatterplots, the relation between Cobb angle on the standing radiograph and mechanical torsion and asymmetry on the 3-D computed tomography scan is shown for the vertebral bodies and intervertebral discs in the thoracic and (thoraco)lumbar scoliotic curves. For significant correlations and linear relations, Pearson's correlation coefficient (*r*) and regression lines are shown.

body in AIS (corrected for the exact anatomical plane) using high-resolution CT data. For quantitative analyses of the 3-D morphology of *in vivo* structures, CT can be considered as the gold standard acquisition technique.[180] With this technique, we observed at least three times more deformation in the discs than in the vertebral bodies in all three dimensions in all scoliotic curves.

AIS normally consists of an upper thoracic, main thoracic and (thoraco)lumbar curve and two junctional segments in-between. In this study, it was observed that all individual AIS curves were longer anteriorly than posteriorly and rotated both between as well as within vertebrae in the axial plane. This *rotated lordosis*, has been described by a number of authors,[34, 35, 37, 38] leading to the hypothesis that lordosis is the initiating deformity and that scoliosis is the result of a disturbed anterior *versus* posterior growth process.[56, 57, 187, 208] While anterior 'overgrowth' of the discs *versus* vertebrae in the sagittal plane has not been studied before, our results on the true coronal asymmetry are in line with previous studies on conventional anterior-posterior radiographs of AIS patients: Most authors observed simultaneous progression of vertebral body and disc wedging in AIS[197, 198, 201, 203], especially around the apices[199, 201]. Unfortunately, these studies did not take into account the fact that each vertebra and disc is rotated and tilted in a different way. Furthermore, those coronal wedge angles were not normalized for the relative size of the discs as compared to the vertebral bodies. In addition, geometrical torsion (also known as intervertebral rotation) can be estimated on the radiographs, but accurate quantification of the mechanical torsion (also known as intrinsic torsion or intravertebral rotation) is impossible on conventional radiographies. In our 3-D study – in which we corrected for the 3-D orientation – the discs were significantly more affected than the vertebrae in terms of anterior length in the true sagittal plane and wedging in the true coronal plane. In the axial plane, the discs were also more affected by torsion than the vertebral bodies. In contrast to coronal and sagittal asymmetry, torsion tended to be greatest in the transitional discs in-between the apical zones. These findings support that AIS is mainly a 3-D deformity of the discs, suggest that abnormal vertebral growth is, according to Hueter-Volkmann's law, rather a consequence than a cause of the deformity.[172, 173]

Although this study was not conducted in a longitudinal design, we believe that the fact that overall 3-D deformation is directly related to Cobb angle is representative for the morphological changes occurring in the discs and vertebrae during progression of AIS. We included all primary and compensatory, structural and non-structural curves and thoracic and (thoraco)lumbar curve patterns to cover the complete spectrum of curve severities and AIS phenotypes. However, because CT scans were obtained of patients that were indicated for surgery, there is risk for selection bias. In this study, asymmetry and torsion was greater in curves with larger Cobb angle. The individual contributions of the discs and vertebrae to the spinal deformity, however, did not significantly change with increasing Cobb angle. Therefore, it seems that the deformation of the discs is a uniform process during the progression of idiopathic scoliosis.

The importance of sagittal spino-pelvic alignment and the axial plane in the etio-pathogenesis of AIS was demonstrated by several investigators over the last decades.[5, 8, 34, 35, 38, 209] We consider scoliosis as a rotatory instability of the spine, the development of AIS depends on disturbance of the delicate balance between rotational stiffness of the spine on the one hand, and rotation inducing forces on the other.[5] Once the spine decompensates into rotation around the stiff posteriorly located ligamentous axis, the vertebral bodies swing farther away from the midline than the posterior structures. At that point by definition a lordosis starts to develop, leading to greater anterior length of the spine. Porter, Guo et al. and Chu et al. showed that the anterior spinal column is significantly longer than the posterior elements or spinal canal in AIS. Their findings have led to alternative hypotheses that anterior spinal overgrowth or a 'too-short' spinal cord can cause AIS.[56, 57, 187] In the present study, however, we differentiated between anterior overgrowth of the vertebrae and the deformity in the discs and we found that the discs were relatively more wedge shaped than the vertebral bodies, furthermore this phenomenon varies within the regions of the spine. Therefore, it is more likely that these are passive phenomena, and that the greater contribution of the discs is caused by the decreased stiffness of intervertebral fibrocartilage as compared to bony vertebrae.

In conclusion, the intervertebral discs contribute more to the 3-D deformity in AIS than the vertebral bodies. Because the processes of torsional deformation, anterior overgrowth and coronal wedging are greater in the discs than the vertebral bodies and are uniform in primary as well as compensatory AIS curves, it appears more logical that these morphological modifications are rather a consequence (amongst others through Hueter-Volkmann's law) than a cause of the deformity.[172, 173, 210, 211]

Chapter 10

Surgical Strategies to Address the True 3-D Deformity in Adolescent Idiopathic Scoliosis

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Adapted from: Biomechanics of the thoracic spine after multi-level, step-wise posterior releases.

ABSTRACT

Study Design: Experimental study.
Objectives: To evaluate the effect of stepwise resection of posterior spinal ligaments, facet joints (i.e. Ponte osteotomies), and ribs on thoracic spinal flexibility.
Summary of Background Data: Removal of posterior ligaments and facet joints and rib releases are techniques used to increase spinal flexibility in corrective spinal surgery for deformities such as idiopathic scoliosis. Clinical results are promising but biomechanical substantiation on this subject is lacking.
Methods: Ten fresh-frozen human cadaveric thoracic spinal specimens (T6-T11) were obtained for biomechanical analysis. A spinal motion simulator applied a pure moment of ±2.5 Nm in flexion, extension, lateral bending (LB) and axial rotation (AR). Range of motion (ROM) was measured for the intact spine and measured again after stepwise resection of the supra- and interspinous ligaments, inferior facet, flaval ligament, superior facet, and ribs.
Results: Supra- and interspinous ligament resection increased ROM in flexion (10.2%) and AR (3.1%) as compared to intact segments. Inferior facetectomy and flavectomy provided an additional significant increase in flexion (4.1%), LB (3.8%) and AR (7.7%), and in flexion (9.1%) and AR (2.5%), respectively. Sequential superior facetectomy only significantly increased ROM in flexion (6.3%). Additional flexibility was gained after rib release in flexion (6.3%), LB (4.5%) and axial rotation (13.0%). Individual releases had no significant effect on ROM in extension.
Conclusions: Different steps in the posterior release of the spine led to an incremental increase in spinal flexibility, but each sequential step had less effect. As compared to ligamentous resection and inferior facetectomy, superior facetectomy (i.e. Ponte osteotomy) improved flexibility in flexion (restoring kyphosis) by 6.3%, an increase of 29.9% vs. 23.6%. Ponte osteotomy did not increase axial rotation and lateral bending flexibility. As blood loss and risks of nerve root damage increase by each subsequent step, the routine use of complete Ponte osteotomies in scoliosis surgery should therefore only be considered for harmonious 3-D alignment of severe spinal deformities.

INTRODUCTION

Adolescent idiopathic scoliosis is a complex three-dimensional deformity of the spine, characterised by a lateral deviation in the coronal plane, rotation in the axial plane and alterations of the sagittal profile. During surgical correction of a scoliotic deformity, surgical releases are often performed to increase spinal flexibility and improve deformity correction. Over the past years, the posterior-only approach to the spine has gained popularity and modern spinal surgery for thoracic idiopathic scoliosis include Ponte-type osteotomies and rib releases in order to restore natural spinal alignment.[212-217] Although only recently used in the surgical treatment of idiopathic scoliosis, the Ponte or Smith-Petersen osteotomy was first described by Smith-Petersen in 1945 for the correction of thoracic kyphosis resulting from ankylosing spondylitis.[218] Ponte described a similar procedure for correcting the sagittal-plane deformity associated with Scheurmann's kyphosis.[215] Both techniques involve the resection of the supraspinous, interspinous and flaval ligament, and the facet joint. More recently, the use of these releases has been described not only for correcting kyphosis but also for correcting coronal and transverse plane deformity.

Clinical series reported promising results using different releases in the surgical treatment of challenging spinal deformities.[214, 219] Nevertheless, the effectiveness of Ponte osteotomies in gaining spinal flexibility compared to less extensive techniques is not proven. This is illustrated by Halanski et al. who reported that Ponte osteotomies increased operative time and blood loss without a significant improvement in correction of adolescent idiopathic scoliosis, as compared to inferior facetectomies alone.[220]

To date, several biomechanical studies assessed the contribution of posterior spinal elements to spinal stability.[221-225] Sangiorgio et al. investigated the effect of complete Ponte osteotomies on spinal motion compared to the intact spine and reported an increase in thoracic range of motion in flexion (69%), extension (56%) and axial rotation (34%), but little effect on lateral bending (2%).[226] The Ponte osteotomy involves multiple steps, including the resection of the posterior spinal ligaments and facet joints. To our knowledge, the individual contribution of resection of each of these structures on spinal flexibility has not been investigated before. Consequently, it remains unclear how much spinal mobility can be gained by each individual step of the release. Feiertag et al. and Yao et al. reported an increase in rotational spinal flexibility after rib mobilisations. However, none of these studies combined rib mobilisations with Ponte osteotomies, and so it is not known whether rib mobilisations provide additional flexibility compared to a Ponte osteotomy alone.[222, 223]

The main goal of this study was to quantify the contribution of each subsequent step of a posterior Ponte osteotomy on thoracic spinal flexibility. In addition, we investigated the possible further gain in flexibility with bilateral rib removal.

METHODS

Specimens and specimen preparation

Twenty-three human thoracic spinal segments (T6-T11) were harvested from freshly frozen (−20°C) human cadavers (mean age 73.5, ± 21.2 years). Spinal specimens with bridging osteophytes or collapsed intervertebral disc spaces (as seen on anteroposterior, lateral and oblique radiographs), previous spinal surgery, ankylosing spondylitis and spinal metastatic disease were excluded.

The spines were thawed twelve hours before testing in 0.9% saline-soaked gauzes to prevent dehydration. Excessive muscle tissue was carefully removed, keeping the spinal ligaments, the facet joints, the costovertebral capsular ligaments and the posterior 5 cm of the ribs intact. Throughout the experiment, the spinal specimens were kept moist with 0.9% saline.

The top and bottom vertebrae (T6 and T11) were potted in a casting-mold and partially buried in a low melting point (48 °C) bismuth alloy (Cerrolow-147; 48.0% bismuth, 25.6% lead, 12.0% tin, 9.6% cadmium, and 4.0% indium). The T6 and T11 vertebrae were fixed securely into the alloy by adding screws into the vertebral body. All articulating parts were kept free.

Biomechanical testing

The test setup was described and validated previously.[227] Before testing, a compressive axial preload of 250N was applied for 1 hour to obtain physiological conditions in the intervertebral disc.[227] Mechanical testing started immediately after the preloading period. Throughout testing, no compressive load was applied to prevent buckling of the spine. Thoracic spines were placed horizontally in a custom made 4-points bending device (Figure 1) in which pure moments in flexion and extension (FE), lateral bending (LB) and axial rotation (AR) can be applied, using a hydraulic materials testing machine (Instron©, model 8872; Instron and IST, Norwood, Canada). In accordance with literature for biomechanical testing of thoracic spines, loads were increased to +2.5Nm at an angular velocity of 0.5 degrees/s.[228] At +2.5 Nm, loading was reduced, again at 0.5 degrees/s, to reach −2.5Nm. To minimise viscoelastic effects, each movement direction was tested for ten subsequent cycles.[229]

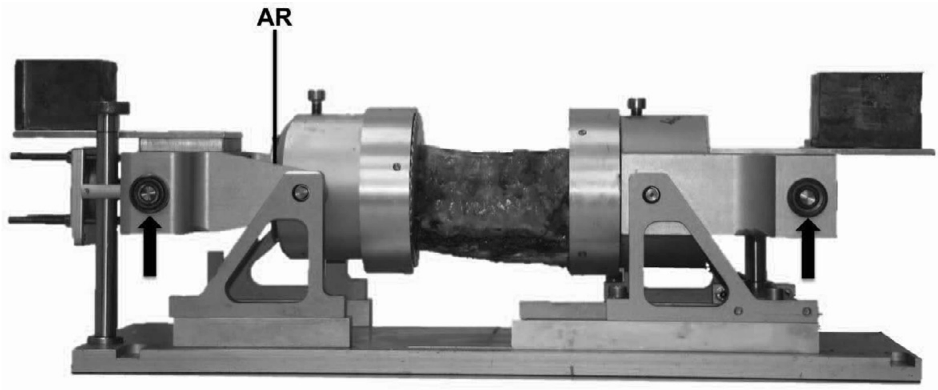

Figure 1. The experimental setup showing the thoracic spinal specimen (T6-T11) positioned in the 4-points bending device. A materials testing machine applied loads to the two points denoted by the arrows. The specimen was rotated 90° to test lateral bending. To test axial rotation, the left cup was rotated using a steel cable powered by the materials testing machine (AR).

Force and displacement of the Instron© machine were recorded and digitized at 100 Hz (Instron© Fast Track 2). All tests were performed at room temperature. The first five segments were tested in the order: FE-LB-AR while the second five segments were tested in the order: AR-FE-LB, in order to correct for order effects. The time between each loading direction, needed for adjusting the test setup, was approximately 5 minutes.

Testing conditions

Biomechanical testing was first performed on the intact spinal specimens and repeated after each destabilisation procedure at levels T7-T10. The sequence of successive release procedures before mechanical testing was as follows:

1. Intact
2. Resection of the supraspinous ligament and interspinous ligament (SL & IL)
3. Bilateral inferior facetectomy (IF)
4. Resection of the flaval ligament (FL)
5. Bilateral superior facetectomy (SF)
6. Rib removal (RR)

Data Analysis

The range of motion (ROM) of the entire spinal specimen was calculated using load-displacement data of the Instron©. The test setup utilises pure moments as the input and therefore produces the same moment at all the spinal levels. This moment is not affected by an alteration in the spinal specimen, such as the removal of a posterior element. Thus, the response at the non-operated spinal levels due to the surgical destabilisation was not affected, as previously described by Panjabi.[230] Therefore, the change in ROM of the whole spinal specimen (T6-T11) after surgical release represented the change in ROM of the three operated motion segments (T7-T8, T8-T9 and T9-T10).

In accordance to recent literature, ROM data of the tenth cycle was analysed.[229] For each direction (FE, LB and AR) the ROM was calculated from load-displacement data using Matlab (Mathworks©, Natick, MA, USA). The ROM was calculated between −2.5Nm and +2.5Nm. For flexion and extension, ROM was also calculated between −2.5Nm and 0Nm, and between 0Nm and +2.5Nm. Each spinal specimen acted as its own internal control, to account for any interspecimen differences in ROM.

Statistical analysis

One-way repeated-measures analysis of variance (ANOVA) and Holm-Sidak multiple paired comparisons were used to assess the effect of each condition of sequential destabilisation on the increase in ROM (% to intact) of the specimens. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Thirteen of twenty-three (56%) available specimens were excluded after radiologic assessment for degeneration and spinal disease, resulting in ten healthy non-degenerated specimens available for biomechanical analysis. The mean absolute and relative ROM (as a percentage to intact testing condition) in all loading directions after each sequential

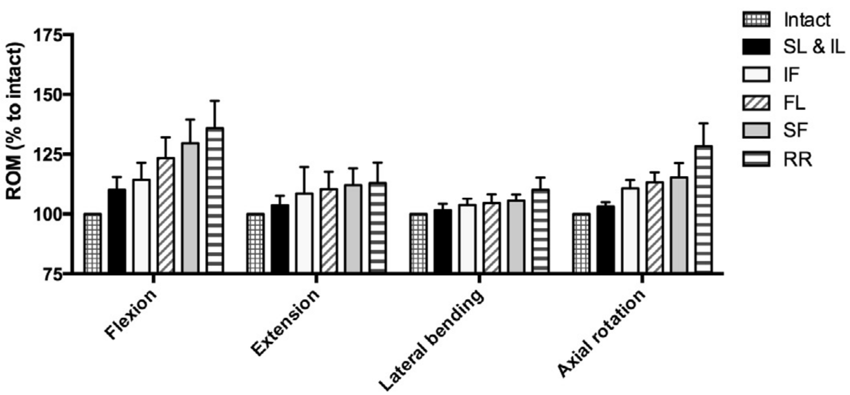

Figure 2. Change in range of motion (% to intact) of the thoracic spinal specimens as a result of sequential release of spinal structures. SL & IL = supraspinous and interspinous ligament resection; IF = inferior facetectomy; FL = flaval ligament; resection; SF = superior facetectomy; RR = rib removal. Range of motion (ROM) is shown separately under flexion, extension, lateral bending and axial rotation. Error bars indicate standard deviations.

Table 1a. Range of motion (degrees) in flexion of thoracic spine segment (T7-T10). SD = standard deviation. SL & IL = supraspinous and interspinous ligament resection; IF = inferior facetectomy; FL = flaval ligament; resection; SF = superior facetectomy; RR = rib removal.

Measure	Flexion (degrees)					
	Intact	SL & IL	IF	FL	SF	RR
Mean	6.4	7.0	7.3	7.8	8.1	8.5
SD	3.4	3.6	4.0	3.8	3.6	3.6
Range	3.8-15.8	4.6-16.9	4.7-18.5	5.4-18.3	5.4-18.1	5.6-18.2

Table 1b.

Measure	Extension (degrees)					
	Intact	SL & IL	IF	FL	SF	RR
Mean	3.9	4.1	4.3	4.4	4.4	4.5
SD	1.4	1.6	1.7	1.7	1.7	1.8
Range	2.1-6.5	2.1-7.0	2.2-7.2	2.2-7.4	2.1-7.6	2.1-7.7

Table 1c.

Measure	Lateral bending (degrees)					
	Intact	SL & IL	IF	FL	SF	RR
Mean	15.5	15.7	16.1	16.2	16.4	17.0
SD	6.5	6.5	6.8	6.7	6.9	7.0
Range	7.2-31.0	7.5-31.1	7.6-32.4	7.5-31.8	7.4-32.8	7.8-33.2

Table 1d.

Measure	Axial rotation (degrees)					
	Intact	SL & IL	IF	FL	SF	RR
Mean	20.8	21.4	23.0	23.5	24.2	27.0
SD	5.9	6.1	6.7	7.0	7.8	9.1
Range	12,6-31.2	13.5-32.2	14.8-34.7	15.2-35.9	13.4-36.9	14.2-41.2

release is presented in Table 1a-1d and Figure 2, respectively. Probability values derived from statistical comparisons of ROM (% to intact) between each testing condition are presented in Table 2.

Flexion

In flexion, resection of the SL & IL complex resulted in a 10.2% increase of the ROM (P=0.0015). Sequential inferior facetectomy exhibited an additional increase of 4.1% (+14.3% as compared to the intact condition) (P=0.0208). A further increase of 9.1% was observed after flaval ligament resection (P=0.0029). Superior facetectomy provided a 6.3% increment (P=0.0045), and successive rib release provided a similar increase of 6.3% (P=0.0015).

Table 2. Probability values from statistical comparisons between ROMs (% to intact) of each testing condition. SL & IL = supraspinous and interspinous ligament resection; IF = inferior facetectomy; LF = flaval ligament resection; SF = superior facetectomy; RR = rib removal. Data is presented separately for flexion, extension, lateral bending and axial rotation.

	SL & IL	IF	FL	SF	RR
Flexion					
Intact	**0,0015**	**0,0011**	**0,0001**	**<0,0001**	**<0,0001**
SL & IL		**0,0208**	**0,0001**	**0,0001**	**<0,0001**
IF			**0,0029**	**0,0015**	**0,0006**
FL				**0,0045**	**0,0015**
SF					**0,0015**
Extension					
Intact	0,2082	0,3259	**0,0214**	**0,0068**	**0,0171**
SL & IL		0,4842	**0,0067**	**0,0018**	**0,0067**
IF			0,7800	0,4842	0,4003
FL				0,4601	0,3817
SF					0,7800
Lateral bending					
Intact	0,2898	**0,0122**	**0,0202**	**0,0014**	**0,0017**
SL & IL		**0,0194**	**0,0194**	**0,0097**	**0,0004**
IF			0,2898	0,0983	**0,0045**
FL				0,2898	**0,0004**
SF					**0,0097**
Axial rotation					
Intact	**0,0023**	**<0,0001**	**<0,0001**	**0,0002**	**<0,0001**
SL & IL		**<0,0001**	**<0,0001**	**0,0023**	**0,0004**
IF			**0,0016**	0,1287	**0,0023**
FL				0,3753	**0,0046**
SF					**<0,0001**

Extension

In extension, no significant increases in ROM were observed after the resection of the SL & IL (P=0.2082) complex, inferior facetectomy (P=0.4842), and resection of the flaval ligament (p=0.7800). Similar observations were made after sequential superior facetectomy (P=0.4601) and rib release (P=0.7800).

Lateral bending

No significant increase in ROM was observed after surgical release of the SL & IL complex in lateral bending. Successive inferior facetectomy resulted in a significant increase in ROM of 3.8% as compared to intact (P=0.0122). Flaval ligament resection and sequential superior facetectomy neither resulted in an increase (P=0.2898, and P=0.2898). Sequential rib release did exhibit an additional increase of 4.7% (P=0.0097).

Axial rotation

Following SL & IL resection, a significant increase of 3.1% (P=0.0023) in ROM was observed. Added inferior facetectomy caused an additional 7.7% increment, and flaval ligament resection brought an extra 2.5% increase (P<0.0001). Successive superior facetectomy did not exhibit any increase in ROM (P=0.3753). Sequential rib release did bring a significant additional increase of 13.0% in ROM (P<0.0001).

DISCUSSION

Adolescent idiopathic scoliosis is a complex three-dimensional deformity of the spine, characterised by lateral deviation in the coronal plane, rotation in the axial plane and extension of the spine (apical lordosis) in the true sagittal plane.[1, 231] Modern scoliosis surgery aims to correct this scoliotic deformation in all three planes, by translation, derotation and posterior lengthening of the spine, thus restoring the natural spinal alignment. Removal of posterior elements is used in order to increase flexibility to allow better correction of the deformation. Clinical results are promising but biomechanical substantiation on this subject is lacking. In order to understand the contribution of different steps in the posterior release, we investigated the ROM after subsequent posterior releases and rib mobilisations in an experimental setup in a sequential order.

We found that the ROM in flexion (kyphosis) and axial rotation increased after resection of the supra- and interspinous ligaments (10.2% and 3.1%, respectively), inferior facets (4.1% and 7.7%, respectively) and flaval ligament (9.1% and 2.5%, respectively). Sequential superior facetectomy only provided a small additional increase in flexion flexibility, and no increase in rotation flexibility.

One of the techniques used during surgery is vertebral derotation.[232-236] This technique is often used after Ponte osteotomies have been performed, which are believed to increase axial rotational flexibility, and thus making the derotational manoeuvre more effective. In the present study, the axial rotation represents this vertebral derotation. After the subsequent resection of the supraspinous, interspinous and flaval ligaments as well as the inferior facet, a superior facetectomy had no additional value in terms of rotation. A possible explanation is, that due to thoracic facet orientation, without direct contact of the two surfaces of the facet joint or restraining joint capsule, a superior facetectomy after an inferior facetectomy is not likely to result in an increase in axial rotation mobility.

The posterior 5 cm of the ribs were left attached to the specimens (so the ribcage was not intact), and rib removal increased axial rotation ROM after the Ponte osteotomies with 13.0% (0.9° per spinal segment). The effect during surgery in a real patient would probably be much larger, with the large stabilising effect of the chest diminished after rib resections. These findings suggest that in severe thoracic deformation cases, if Ponte osteotomies fail to induce sufficient spinal mobility, an additional increase in rotational spinal flexibility can be obtained by performing rib mobilisations.

To date, multiple biomechanical studies have reported significant increases in flexion-extension ROM ranging from 13-45% after complete facetectomies.[224, 225, 237] Therefore, it is often believed that these osteotomies allow for better restoration of sagittal spino-pelvic alignment. However, the effect of a complete facetectomy compared to an inferior facetectomy on the spinal ROM after removal of the supraspinous, interspinous and flaval ligament had not been investigated before. This study shows that including a superior facetectomy contributes an extra 6.3% (0.1° per spinal segment) as compared to flexion ROM after inferior facetectomy only. This is a minor increase compared to the 23.3% (0.5° per spinal segment) increase in flexion already provided by the combined removal of the posterior ligament complex, inferior facet and flaval ligament. From a clinical perspective, Halanski et al. showed that superior facetectomy introduces an increase in blood loss, longer operative time and the risk of nerve root damage, without improving coronal or sagittal correction as compared to inferior facetectomies.[220] From these results and the current study, it seems that an additional superior facetectomy, i.e. full Ponte osteotomy, will hardly help restoring sagittal alignment. Although it is postulated that these osteotomies could be useful in extremely stiff spines in which more posterior lengthening is necessary for optimal correction of the apical lordosis to thoracic kyphosis, Halanski et al. discourage the routine use of Ponte osteotomies.[220]

Besides vertebral derotation and restoration of sagittal alignment, coronal correction is an important goal during surgery. In this study we investigated this effect by applying lateral bending moments to the spinal specimen. Increases of 3.8% and 4.7% were observed after inferior facetectomy and rib mobilisation respectively. Flaval ligament resection and sequential superior facetectomy did not provide any benefit after the inferior facet had been removed.

Resection of the supraspinous and interspinous ligaments, flaval ligament and complete facetectomies (i.e. Ponte osteotomies) increased ROM with 29.6% (1.7° per spinal segment) in flexion, 12.1% (0.5° per spinal segment) in extension, 5.5% (0.9° per spinal segment) in lateral bending and 15.3% (3.4° per spinal segment) in axial rotation. These results are in agreement with findings of a cadaveric study performed by Anderson et al..[225] However, Sangiorgio et al. reported a large increase of thoracic ROM after complete Ponte osteotomies in flexion (69%), extension (56%) and axial rotation (34%), but little effect in lateral bending (2%).[226] Other biomechanical studies reported similar results as Sangiorgio et al..[224, 225] The differences between other studies and our results could be explained by our strict selection of non-degenerative spines. 56% of the available spinal specimens were excluded in this study, whereas the previously discussed literature did not report such selection criteria. Future experimental studies focussed on non-degenerative spinal disorders should perform prior radiologic assessment to exclude degenerated spinal specimens, to make it easier to translate the acquired results to the clinical situation.

One of the limitations of this study is the advanced age of the specimens used. To limit the effect of age, we only used spinal specimens devoid of intervertebral disc degeneration and bridging osteophytes. Additionally, due to technical limitations of our testing setup we could only keep the posterior 5 cm of the ribs intact and not the whole ribcage. As a result, the stabilising effects of the rib cage and trunk muscles were not accounted for. Another limitation is that due to the limited amount of spinal specimens available, we could not randomise the order of the surgical releases. The order was chosen to represent the technique as is commonly used in surgical practise for spinal scoliotic deformities. The effects of each step of the surgical releases could differ if a different order was chosen. Lastly, we were unable to obtain adolescent spinal specimens with scoliotic deformities, which influences the translation of the results found in this study into clinical practice. Besides these limitations, this study provides important data concerning spinal releases, and the results are in line with clinical studies.[220]

This study demonstrates that posterior spinal releases used in scoliosis surgery follow the law of diminishing returns: removing more posterior spinal structures does not automatically result in an increase of spinal flexibility. It can therefore be concluded that ROM in flexion, lateral bending and axial rotation increases by resection of the supraspinous and interspinous ligaments, inferior facet and flaval ligament. Superior facetectomy, however, provided only a small additional increase in flexion (kyphosis) and had no value for range of motion in extension, lateral bending and axial rotation.

We believe that this study holds the following clinical relevance. Extensive posterior surgical release may increase blood loss, operative time and the risk of nerve root damage. Based on this data we propose that it is not necessary to perform a full Ponte osteotomy in routine scoliosis surgery. In severe cases of spinal deformity, Ponte osteotomies or rib mobilisations could provide additional spinal flexibility for posterior distraction and derotational manoeuvres, respectively.

Chapter 11

Reliability and Validity of the Adapted Dutch Version of the revised Scoliosis Research Society 22-item Questionnaire

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ABSTRACT

Background context. As in other fields of medicine, there is an increasing interest among orthopedic surgeons to measure health-related quality of life in adolescent idiopathic scoliosis patients, to evaluate the burden of disease and the effectiveness of different treatment strategies. The development of the revised Scoliosis Research Society 22-item patient questionnaire (SRS-22r) enabled a comprehensive evaluation of health-related quality of life of these patients. Over the years, the SRS-22r gained wide acceptance and this questionnaire has been used in several different countries, different languages and cultures. The SRS-22r has not been translated into Dutch to date.

Purpose. To translate the SRS-22r into Dutch and adapt it cross-culturally as outlined by international guidelines, and to test its psychometric properties to measure health related quality of life of adolescent idiopathic scoliosis patients in the Netherlands.

Study Design/Setting. A cross-sectional, multicenter validation study.

Patient sample. 135 adolescent idiopathic scoliosis patients (mean age 15.1 years old) of three major scoliosis centers in the Netherlands were enrolled in this study. Ninety-two (68%) subjects completed the Dutch SRS-22r, Child Health Questionnaire-CF87 (golden standard for adolescents) and SF-36 (golden standard for adults). Two weeks later, seventy-three (79%) of ninety-two respondents returned a second SRS-22r. Demographics, curve type, Risser's stage and treatment status were documented.

Outcome Measures. Floor and ceiling effects, internal consistency, reproducibility, concurrent validity and discriminative ability of the Dutch version of the SRS-22r questionnaire.

Methods. For content analysis, SRS-22r domain scores (function, pain, self-image, mental health and satisfaction with management) were explored and floor and ceiling effects were determined. Cronbach's α was calculated for internal consistency of each domain of the questionnaires and reproducibility was assessed by test-retest reliability analysis. Using Pearson's correlation coefficient, comparison of the domains of the Dutch SRS-22r with the domains of the SF-36 and Child Health Questionnaire-CF87 assessed the concurrent validity. Differences in SRS-22r domain scores between untreated patients with different curve severity determined the discriminative ability of the questionnaire.

Results. The SRS-22r domains, as well as the SF-36 and CHQ-CF87 domains, demonstrated no floor effects, but the function, pain and satisfaction with management domains had ceiling effects, indicating the proportion of subjects with the maximum score, between 19.6% and 33.0%. Internal consistency was very satisfactory for all SRS-22r domains: Cronbach's α was between 0.718 and 0.852. By omitting question 15, the internal consistency of the function domain increased from 0.746 to 0.827. Test-retest reliability was ≥0.799 for all SRS-22r domains. The function, pain, mental health and self-image domains correlated under the 0.001 significance level with the correspond-

ing CHQ-CF87 and SF-36 domains. The satisfaction with management domain did not correlate with the other questionnaires. The SRS-22r had the ability to detect differences between groups with different curve severity; patients with a severe scoliotic curvature had significantly lower pain and self-image domain scores than patients with relatively mild scoliosis.
Conclusions. The Dutch SRS-22r had the properties needed for the measurement of patient perceived health-related quality of life of adolescent idiopathic scoliosis patients in the Netherlands. The Dutch SRS-22r could be used for the longitudinal follow-up of adolescent idiopathic scoliosis patients from adolescence to adulthood and for establishing the effects of conservative or invasive surgical treatment.

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a deformity of the spine and trunk in previously healthy children of unknown etiology.[2] As a consequence of the deformity, especially immature children with progressive curves could suffer from severe physical symptoms (back pain, diminished back mobility and decreased lung function) and psychosocial symptoms (body image issues and diminished self-esteem).[46, 238] Even without severe progression, when the curves are usually not life threatening and no brace or surgical treatment is used, the deformity may interfere with daily life and might have significant effects on health-related quality of life. While the most common scoliosis treatments, bracing and surgery, aim to prevent progression of the spinal curvature and to improve the symptoms, evaluations of effectiveness are in many instances mainly based on radiographic measurements of the curvature.[239, 240] The effectiveness in terms of health-related quality of life, however, are probably more important and often remain relatively under-exposed.

The development of the Scoliosis Research Society (SRS) patient questionnaire enabled a comprehensive evaluation of the health-related quality of life of AIS patients. The original SRS 24-item questionnaire, a simple, practical and discriminative disease-specific questionnaire as developed by Haher et al., aimed to facilitate the assessment of clinical outcome after treatment of AIS. This questionnaire consisted of 24 questions and measured four domains: *pain*, *self-image*, *function*, and *satisfaction with management*.[241] Because of a number of concerns and shortcomings regarding its psychometric properties, a series of modifications and refinements led, through the SRS 23-item questionnaire, to the development of the SRS 22-item questionnaire (SRS-22) in 2000; The *function*, *pain*, *self-image* and *mental health* domains consisted of five questions and the *satisfaction with management* domain of two questions.[242] In 2005, Asher et al. improved internal consistency by a minor revision of question 18, resulting in the current revised SRS 22-item questionnaire (SRS-22r).[59] Over the years, especially the SRS-22 and SRS-22r gained wide acceptance and these questionnaires were translated and adapted into seventeen different languages and/or cultures.[243-260] The SRS-22 was previously translated into Dutch and adapted cross-culturally to the Netherlands by Bunge et al., but the psychometric properties were never completely investigated.[261] To date the SRS-22r has not been translated into Dutch whereas there is a great need from both a clinical and research perspective. The aims of this study are to translate the original SRS-22r into Dutch, to adapt it to the Dutch culture, and to test its properties for evaluation of health-related quality of life of AIS patients in the Netherlands.

METHODS

Guidelines for cross-cultural adaptation and validation of self-reported health status measures as outlined by Beaton et al. were used for this study.[262]

Cross-cultural adaptation and translation process

The translation process consisted of four stages, followed by pre-testing and final validity and reliability analysis. First, an orthopedic researcher (MD), informed for the study procedure, and uninformed technical student translated the original English SRS-22r into Dutch.[59] The translators had Dutch as mother tongue and translated independent of each other. Second, the translators and a recording observer merged the two translations and the Dutch version of the SRS-22 questionnaire.[261] For any discrepancy, consensus was reached by discussion. Third, two independent, uninformed bilingual translators with English as mother tongue (resident general surgery and technical PhD-student) performed a translation back from Dutch into English. They were blinded for the original SRS-22r questionnaire to avoid information bias. Fourth, during an expert committee meeting, the translators, back translators, a professor of spinal surgery, a recording observer, an experienced epidemiologist and a professional translator (English-Dutch and Dutch-English) reviewed all translations and written reports of the different stages as well as the original questionnaire. Equivalence of the pre-final version and original English SRS-22r was examined for semantics, idioms and conceptual meaning. The expert committee discussed the translations and adaptations, and developed a pre-final version of the Dutch SRS-22r.

Pre-final testing

Thirty-one consecutive Dutch-speaking AIS patients between 10 and 18 years old (23 girls, 8 boys) completed the pre-final version of the Dutch SRS-22r in the outpatient clinic of a tertiary spine center (Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands). Before the pre-final testing and final testing, approval of the institutional review board and Medical Ethics Committee University Medical Center Utrecht was received. The patients were interviewed about their understanding of the questions and answers, and about the difficulties they had encountered. In addition, the duration of completion of the questionnaire assessed the feasibility of administering the test to regular patients. Since the total number of pre-final questionnaires was small, statistical tests were not performed. On the basis of the subjects' comments, the expert committee determined the final version of the questionnaire to be tested.

Study procedures

135 patients with a history of AIS were asked to participate in this validation study and each subject and their parents gave informed consent. The final testing was carried out in the outpatient clinic of three major spine centers in the Netherlands (Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht; Vrije Universteit medisch centrum, Amsterdam; and the Sint Maartenskliniek, Nijmegen) over a period of two months. All AIS patients over 10 years old who had the ability to speak and read Dutch fluently were included. Patients with congenital anomalies, central or peripheral neurological symptoms, or systemic disorders (chronic kidney or liver diseases, tumors, rheumatoid-like diseases or mental/psychiatric disorders) were excluded. On the most recent radiograph of the spine, a trained orthopedic researcher classified the curve type of the deformities, determined Risser's stage and measured the Cobb angles.[39, 41, 122] At the outpatient clinic all participants received the final Dutch SRS-22r, a visual analog scale for pain (VAS; 100 millimeter, score 0-100) and previously validated Dutch versions of RAND 36-item short form Health Survey (SF-36) and the Child Health Questionnaire – Child Form 87 (CHQ-CF87; HealthActCHQ Inc., Cambridge, MA, United States).[263, 264] For the comparability with the other questionnaires in this study, the VAS score was inverted: the maximum score '100' corresponded to no pain and the minimum score '0' to severe pain. They were instructed to complete the questionnaires at home by themselves, without their parents giving them help, and return the forms within a week. The SF-36 and CHQ-CF87 are previously validated, generic health-related quality of life questionnaires for adults (>18 years old) and adolescents (10-18 years old), respectively. In order to test the test-retest reliability, two weeks later, a second final Dutch SRS-22r and a request to return the questionnaire were mailed to all participants. If participants returned the first SRS-22r questionnaire after they received the second SRS-22r, the participants response was not included in the test-retest reliability analysis. The first SRS-22r of these participants, however, was used for other reliability and validity analyses in this study.

Statistical analysis of data

Content Analysis

Scoring of the questions and domains of the SRS-22r, SF-36 and CHQ-CF87 was performed according to the corresponding scoring guidelines.[264, 265] Scoring of the SRS domains was equal to the original SRS-22r scoring system: total scores were between 5 and 25 for the domains *function*, *pain*, *self-image* and *mental health* (each based on 5 questions), and between 2 and 10 for *satisfaction with management* (based on 2 questions); the average scores varied between 1 (minimum score) and 5 (maximum score) for all domains. For content analysis, data were explored (mean, standard deviation and range) and checked for outliers. In addition, floor and ceiling effects (>10% with minimum or maximum possible score, respectively) were calculated.

Reliability

Cronbach's α assessed the internal consistency of each SRS-22r, SF-36 and CHQ-CF87 domain and was checked for variation if a question was omitted. Cronbach's α<0.70 indicated 'poor' internal consistency, Cronbach's α between 0.70 and 0.80 was 'good' internal consistency, and Cronbach's α>0.80 was 'excellent' internal consistency. Reproducibility of each SRS-22r domain score was assessed by test-retest reliability analysis of the first and second SRS-22r using the intraclass correlation coefficient (ICC). ICC's between 0.70 and 0.80 indicated 'good' and ICC's >0.80 'excellent' reliability.

Concurrent validity

For the study of concurrent validity, the mean scores of each domain of the Dutch SRS-22r were compared with the domains of the SF-36, CHQ-CF87 and VAS for pain. 'Poor', 'good' and 'excellent' concurrent validity was defined as a Pearson's correlation coefficient less than 0.50, between 0.50 and 0.70, and more than 0.70, respectively.

Discriminant ability

Two subsets of patients with different clinical variables who had no treatment for their curve to date were determined prior to starting the discriminant ability analysis. The first group was made of patients with a mild curve (Cobb angle less than 30 degrees) which are normally asymptomatic. The second group consisted of patients with a moderate or severe curve (Cobb angle more than 30 degrees). Patients with a history of brace therapy or scoliosis surgery were excluded in the discriminative ability analysis. The ability of the questionnaire to detect differences between those two groups was tested. The three participating centers had a joint guideline for treatment of idiopathic scoliosis when this study was performed.

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, United States). Cronbach's α, ICC (two way random model with absolute agreement) and *r* were used to asses internal consistency, reproducibility and concurrent validity of the Dutch translation of the SRS-22r questionnaire, respectively. If $P<0.001$, the correlation with generic CHQ-CF87 and SF-36 questionnaires was statistically significant. Independent samples t-tests (significance level 0.05) - were used to evaluate differences in SRS-22r domain scores between the two subgroups of untreated subjects.

RESULTS

Pre-final testing

At pre-final testing the majority of the patients understood the questions and answers completely, responded to all questions and completed the questionnaire within ten minutes. However, the expert committee adapted four questions (9, 16, 21 and 22) by minor changes because of difficulties that were encountered during the interviews. Due to the limited mathematical level and vocabulary of 10 and 11 year old AIS patients, the answers in percentages of question 9 were replaced by a commonly used ordinal scale for ability/disability, and in question 16 the Dutch phrasing of "down hearted and blue" was replaced by an easier word. To allow for examination of AIS patients who were under observation, 'treatment' in question 21 and 'management' in question 22 were changed into 'regular check-ups and treatment'. Other comments did not require adjustments. The final Dutch SRS-22r questionnaire can be found in the Appendix or on the Scoliosis Research Society website.[265]

Patient sample

Ninety-two (68%) AIS patients completed the first set of questionnaires (Table 1). Seventy-three (79%) of them completed both sets of questionnaires. The average response time between the first and second set of questionnaires was 19.3 (±8.2) days. Table 1 shows the basic clinical characteristics of the respondents. The mean age was 15.1 (±2.0, range 10-21) years and eighty (87%) participants were female. Curve severity differed between 10° and 70° Cobb angle (mean 38°±14°, median 38°). Fifty-one respondents had a thoracic curve (Lenke I and II), sixteen a (thoraco)lumbar curve (Lenke V) and twenty-five a thoracic and lumbar structural deformity (Lenke III, IV or VI).[41] Fifty-three respondents were under observation (Cobb<30°, n=15; Cobb>30°, n=38), twenty under brace treatment and nineteen had undergone operative scoliosis correction (median time since surgery 9 months, range 1-82 months). No significant differences in gender and curve type distribution were observed between the different cohorts.

Table 1. Clinical characteristics of the study population are shown. SD=standard deviation

Clinical characteristics	AIS patients (n=92)	
Women (%)	80	(87)
- Postmenarcheal (%)	62	(67)
Age (±SD)	15.1	(±2.0)
BMI (±SD)	19.6	(±2.8)
Cobb angle (±SD)	38	(±14)
Curve type		
- Thoracic curve (%)	51	(55)
- Thoracic and (thoraco)lumbar curve (%)	25	(27)
- (Thoraco)lumbar curve (%)	16	(17)
Risser stage		
- Stage I (%)	11	(12)
- Stage II (%)	14	(15)
- Stage III (%)	9	(10)
- Stage IV (%)	33	(36)
- Stage V (%)	23	(25)
Treatment		
- Under observation (%)	53	(58)
- Bracing (%)	20	(22)
- Surgery (%)	19	(21)
* Posterior spondylodesis (%)	17	(18)
* Anterior spondylodesis (%)	2	(2)
* Time since surgery in Months (±SD)	18	(±21)

Content analysis

In our study population of 92 AIS patients, the mean domain scores of the final Dutch SRS-22r were between 3.81 and 4.49 (Table 2). The SRS-22r domains, as well as the SF-36 and CHQ-CF87 domains, demonstrated no floor effects. Ceiling effects between 19.6% and 33.0% were observed for the *function*, *pain* and *satisfaction with management* domains of the SRS-22r. The *function* domain of the SRS-22r demonstrated a ceiling effect (33%) comparable to the *physical function* domain of the SF-36 (27%) and CHQ-CF87 (38%), indicating the proportion of subjects with the maximum score. Similarly, the *pain* domain of the SRS-22r demonstrated a lower ceiling effect (20%) than the *bodily pain* domain of the SF-36 (23%), CHQ-CF87 (25%) and the VAS for pain (22%). No ceiling effects were observed for the *self-image* and *mental health* domains of the Dutch SRS-22r, while the corresponding SF-36 and CHQ-CF87 domains showed relatively high ceiling effects (up to 84%).

Table 2. Descriptive statistics are shown for the SRS-22r, SF-36, VAS for pain and CHQ-CF87 questionnaires. SD=standard deviation

Domains	Mean score	SD	Range	% with floor effect†	% with ceiling effect†
SRS-22r					
Function	4.49	0.53	3.20 - 5.00	0	33
Pain	4.04	0.88	1.00 – 5.00	1	20
Self-image	3.81	0.66	2.00 – 5.00	0	4
Mental health	4.05	0.60	2.20 – 5.00	0	8
Satisfaction with management	3.99	0.78	1.50 – 5.00	0	22
SF-36					
Physical function	84.5	16.4	25.0 – 100.0	0	27
Role-Physical	78.3	32.1	0.0 – 100.0	4	62
Bodily Pain	77.4	20.3	10.0 – 100.0	0	23
General Health	73.9	20.6	15.0 – 100.0	0	15
Vitality	70.9	19.4	0.0 – 100.0	1	13
Social functioning	87.8	16.7	25.0 – 100.0	0	52
Role-Emotional	89.7	25.7	0.0 – 100.0	4	83
Mental Health	82.3	14.4	40.0 – 100.0	0	15
VAS for pain*§	72.0	75.0	10.0 – 100.0	0	22
CHQ-CF87					
Behavior	84.5	9.8	57.9 – 100.0	0	3
Bodily Pain	68.1	26.6	0.0 – 100.0	1	25
Family Activity	91.0	10.0	60.0 – 100.0	0	42
Mental Health	79.0	13.4	42.2 – 100.0	0	4
General Health	72.3	17.8	25.4 – 100.0	0	5
Role Function Behavior	96.4	10.2	44.3 – 100.0	0	84
Physical Function	89.6	14.2	18.4 – 100.0	0	38
Role-Emotional	90.8	18.4	11.0 – 100.0	0	70
Role-Physical	92.6	15.2	33.0 – 100.0	0	73
Self-Esteem	75.8	12.4	46.4 – 100.0	0	3
Global Behavior*	79.7	16.6	30.0 – 100.0	0	24
Global General Health*	76.1	20.9	30.0 – 100.0	0	23
Family Cohesion*	81.0	19.0	0.0 – 100.0	1	33
Change in Health*	3.0	1.0	1.0 – 5.0	5	11

† = The floor and ceiling effect is the percentage of subjects that answered the lowest or highest possible score of the questionnaire, respectively: SRS-22r, lowest and highest possible score was 1.0 and 5.0; SF-36, VAS for pain and CHQ-CF87, lowest and highest possible score was 0.0 and 100.0.
§ = The maximum score '100' corresponded to no pain and the minimum score '0' to severe pain.
* = Single item.

Reliability

The statistical analysis showed good results for internal consistency of the SRS-22r domains *function*, *self-image*, *mental health* and *satisfaction with management*, and excellent internal consistency for the domain *pain* (Table 3). If question 15 was omitted, because of a negative correlation with the *function* domain score, Cronbach's α increased to 0.827. The SF-36 domain *social functioning* had poor, *physical function* and *mental health* excellent and all other domains good internal consistency. The internal consistency was excellent for all CHQ-CF87 domains (Cronbach's α between 0.829 and 0.933), except for domain *family activity* (Cronbach's α=0.689). The reproducibility of the *satisfaction with management* domain was good, while the domains *function*, *pain*, *self-image*, and *mental health* demonstrated excellent test-retest results (ICC per domain: *function* 0.861; *pain* 0.929; *self-image* 0.878; *mental health* 0.855; *satisfaction with management* 0.799).

Table 3. Internal consistency of the SRS-22r, SF-36 and CHQ-CF87 domains consisting of more than one item is shown.

SRS-22r domain	Cronbach's α	SF-36 domain	Cronbach's α	CHQ-CF87 domain	Cronbach's α
Function	0.746*	Physical function	0.846	Behavior	0.827
Pain	0.852	Role-Physical	0.784	Bodily Pain	0.933
Self-image	0.718	Bodily Pain	0.792	Family Activity	0.689
Mental health	0.777	General Health	0.798	Mental Health	0.908
Satisfaction with management	0.712	Vitality	0.757	General Health	0.829
		Social functioning	0.635	Role Function Behavior	0.857
		Role-Emotional	0.795	Physical Function	0.860
		Mental Health	0.816	Role-Emotional	0.900
				Role-Physical	0.906
				Self-Esteem	0.884

*If question 15 is omitted, Cronbach's α is 0.827

Concurrent validity

All correlations between the SRS-22r and SF-36 domain scores were under the <0.001 significance level and differed between 0.390 and 0.833 (Table 4). The SRS-22r *function* domain had excellent correlation with the SF-36 domains *physical function* (*r*=0.808) and *role-physical* (*r*=0.717), and with the CHQ-CF87 domain *physical function* (*r*=0.708). The SRS-22r domain *pain* demonstrated excellent correlation with the SF-36 domains *bodily pain* (*r*=0.857) and *physical function* (*r*=0.833), with the CHQ-CF87 domain *bodily pain* (*r*=0.886) and with the VAS score for pain (*r*=0.872). The average *mental health* score of the SF-36 correlated excellent with the *mental health* score of the SRS-22r (*r*=0.787). The SRS-22r domain *self-image* had good correlation with the CHQ-CF87 *general health* score. No correlations were observed for the SRS-22r domain *satisfaction with management*.

Table 4. Concurrent validity was calculated for the SRS-22r domains in relation to the SF-36 domains, CHQ-CF87 domains and VAS score for pain. All statistically significant correlations are shown, ranked by degree of correlation. *r* = Pearson's correlation coefficient, VAS= visual analog score.

SRS-22r domain	SF-36 domain	*r* **	CHQ-CF87 domain	*r* **	VAS	*r* **
Function	Physical function	0.808	Physical Function	0.708	VAS for pain*	0.473
	Role-Physical	0.717	Bodily Pain	0.606		
	Bodily Pain	0.699	Role-Physical	0.570		
	Social functioning	0.502	Family Cohesion*	0.520		
	General Health	0.424	Self-Esteem	0.397		
	Vitality	0.465	General Health	0.386		
			Global General Health*	0.382		
			Mental Health	0.366		
Pain	Bodily Pain	0.857	Bodily Pain	0.886	VAS for pain*	0.872
	Physical function	0.833	Physical Function	0.698		
	Role-Physical	0.694	Role-Physical	0.578		
	Vitality	0.431	Change in Health*	0.463		
	General Health	0.396	General Health	0.441		
	Social functioning	0.390	Global General Health*	0.387		
Self-image	Bodily Pain	0.493	General Health	0.515	VAS for pain*	0.448
	Physical function	0.434	Change in Health*	0.477		
	General Health	0.396	Bodily Pain	0.462		
			Self-Esteem	0.415		
			Global General Health*	0.415		
			Physical Function	0.374		
Mental health	Mental Health	0.787	Mental Health	0.623	VAS for pain*	0.395
	Vitality	0.648	Self-Esteem	0.538		
	Social functioning	0.592	Family Activity	0.502		
	Role-Physical	0.522	Global General Health*	0.499		
	Physical function	0.501	General Health	0.486		
	Bodily Pain	0.492	Role-Emotional	0.476		
	Role-Emotional	0.489	Physical Function	0.434		
	General Health	0.452	Behavior	0.413		
			Bodily Pain	0.413		
Satisfaction with management	No correlations		No correlations		No correlations	

* = single item, ** = correlations are significant at the <0.001 level

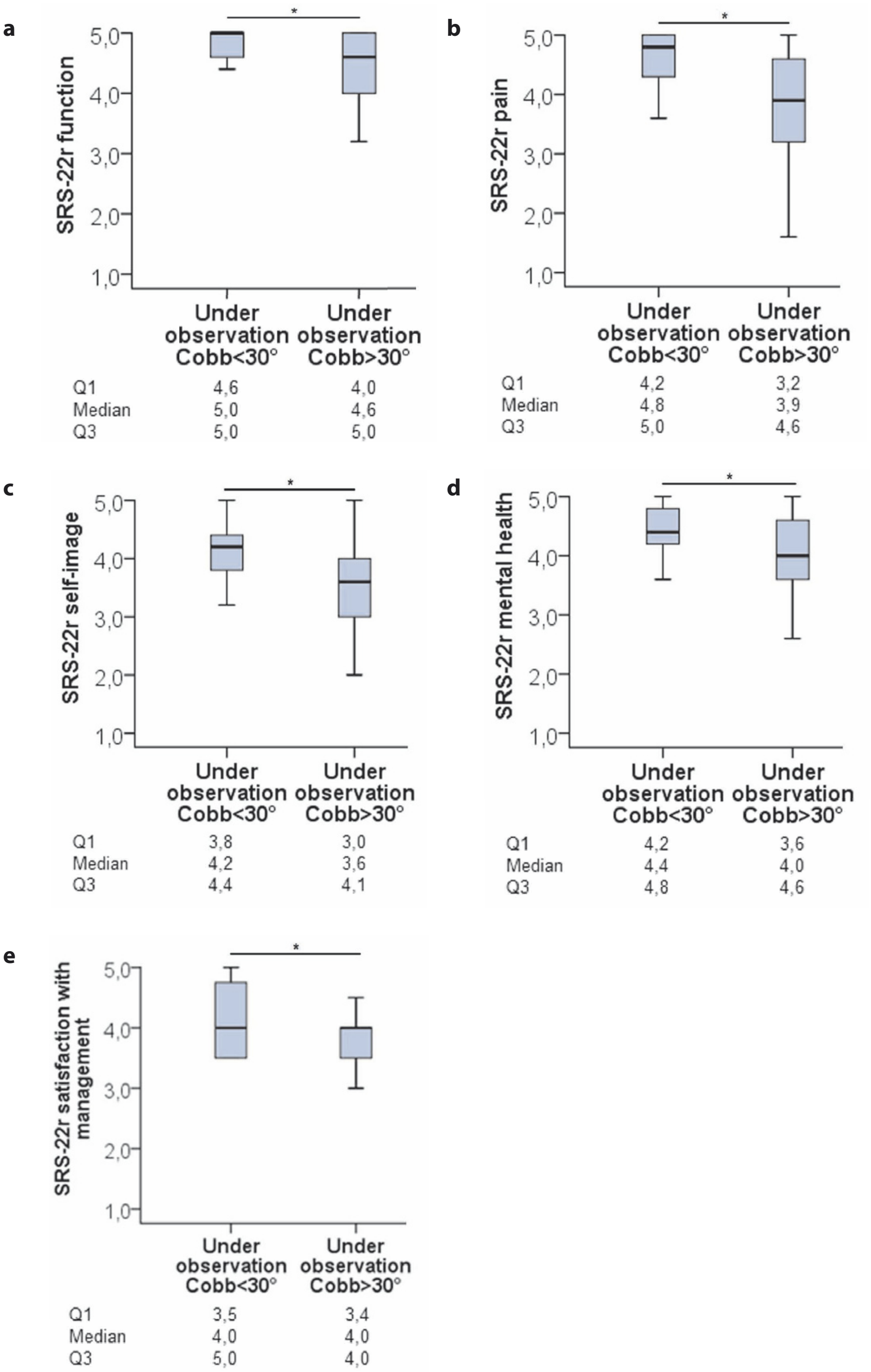

Figure 1. a-e: Box-Whisker plots for the SRS-22r domain scores are presented for two subsets of patients with different curve severities that were under observation. *= differences under the <0.05 significance level.

Discriminative ability

Statistical analysis revealed that participants who were under observation for a mild curve had significantly higher scores in all SRS-22r domains than participants with moderate or severe scoliosis (*function P*=0.002, *pain P*=0.003, *self-image P*=0.004, *mental health P*=0.019, *satisfaction with management P*=0.015) (Table 5; Figure 1), indicating the ability of the questionnaire to discriminate between scoliosis patients with different levels of disease-specific quality of life.

Table 5. Cross-sectional differences are shown for two subgroups of idiopathic scoliosis patients that were under observation. SD=standard deviation

SRS-22r domain	SRS-22r domain	Mean	SD	*% floor effect*	% ceiling effect
Under observation, Cobb<30° (n=15)	*Function*	4,8	0,3	0	53,3
	Pain	4,6	0,5	0	46,7
	Self-Image	4,2	0,5	0	13,3
	Mental Health	4,4	0,4	0	13,3
	Satisfaction with management	4,2	0,6	0	26,7
Under observation, Cobb>30° (n=38)	*Function*	4,5	0,5	0	42,1
	Pain	3,8	1,0	0	21,1
	Self-Image	3,6	0,7	0	2,6
	Mental Health	4,0	0,6	0	7,9
	Satisfaction with management	3,7	0,7	0	5,3
	Satisfaction with management	4,7	0,4	0	57,9

DISCUSSION

The present study describes the cross-cultural translation and adaptation of the original SRS-22r into Dutch, following the international guidelines, and the evaluation of its psychometric properties.[262, 266] The Dutch SRS-22r had very satisfactory reliability, correlated well with generic questionnaires and was useful for the purpose to measure cross-sectional differences between patients with different clinical status. Nowadays the SRS-22 and SRS-22r versions are widely accepted instruments for the measurement of health-related quality of life in scoliosis patients and were previously adapted successfully for the Brazilian[243], Chinese[244-246], French-Canadian[247], German[248], Greek[249], Italian[250], Japanese[251], Korean[252], Norwegian[253], Persian[254], Polish[255], Swedish[256], Spanish[257, 258], Thai[259] and Turkish[260] language and culture. Whether this cross-sectional study provides supportive evidence that the Dutch SRS-22r is a reliable and valid instrument for evaluation of AIS patients undergoing conservative or surgical interventions - in a longitudinal setup - will be discussed.[267]

For the long-term follow-up of AIS patients, it is obvious that an instrument is needed that can be used from adolescence to adulthood. The Dutch SRS-22r correlated well with the corresponding domains of the most widely used generic health-related quality of life questionnaires for adolescents (CHQ-CF87) and for adults (SF-36). These generic questionnaires are in itself less useful for the follow-up of AIS patients, since the SF-36 is not validated for adolescents and the CHQ-CF87 not for adults[263, 264, 268] This is the first complete cross-cultural adaptation and validation study comparing the results of the SRS-22r with a generic questionnaire that was developed for adolescents and with another generic questionnaire for adults. A majority of the researchers of the validation studies of the SRS-22r in different countries and cultures compared their questionnaire to the SF-36 for adults.[243-246, 249-252, 254, 256, 259, 260] In this study the SRS-22r domains were compared to the CHQ-CF87 and SF-36 domains, the correlations of the corresponding domains were very acceptable and the results were similar to the studies of Glattes et al. and Asher et al..[59, 269] Because of the validity of the questionnaire in adolescents and adults, the Dutch SRS-22r has the properties for follow-up of health-related quality of life of AIS patients, irrespective of age, which is lacking for the CHQ-CF87 and SF-36.

In this study the ability to detect minimal clinically important differences and responsiveness of the Dutch SRS-22r has not been investigated completely, because longitudinal data is required for adequate calculations. Our results encourage, however, that the questionnaire is capable of discriminating between AIS patients with different curve severity. As an estimation for clinical important difference, the variability of the *function*, *pain*, *self-image*, *mental health* and *satisfaction with management* domain can be used: 0.71, 1.19, 0.88, 0.83, 0.71, respectively. In future studies, the responsiveness can be obtained by the examination of the mean change as a result of the intervention divided by the variability and can be used for sample size calculations.[267]

The Dutch SRS-22r was able to address physical and psychosocial symptoms that AIS patients could encounter in daily life as indicated by low floor effects.[59] However, ceiling effects were observed in some domains, which might be due to our young population (mean age 15.1, minimum age 10 years) with relatively mild curves (lowest Cobb angle 10°). In a longitudinal study, however, with AIS patient requiring treatment ceiling effects might be reduced, because this study showed lower ceiling effects for AIS patients with more severe curves, similar to the Polish and Thai validation studies.[255, 259]

The contribution of each question to the relevant SRS-22r domain score and the repeatability was tested, and it was optimized to ensure reliability of the Dutch SRS-22r. Previously, discussion of the internal consistency of the *function* domain of the SRS-22 led to the development of the SRS-22r.[270-275] The problem was traced to questions 15 and 18.[246, 257, 258, 260, 270-275] In this study the internal consistency of the *function* domain was already satisfactory, but the reliability of the score increased when question 15 ("Are you and/or your family experiencing financial difficulties because of your back?") was omitted. One of the reasons that question 15 is not in line with the other questions of the *function* domain might be some sort of perception bias, due to the suboptimal ability of adolescent schoolchildren to judge the families financial situation. Other validation studies that encountered problems with the reliability of question 15, as well as this study, included predominantly young adolescent scoliosis patients and no or a few adults.[246, 257, 258, 260] On one hand, the internal consistency is slightly higher if question 15 is omitted. On the other hand, for over-time measurements from childhood to adulthood and for better comparability with many other versions around the world (in which question 15 is included in the scoring), it might be better to include question 15 in the scoring of the Dutch SRS-22r's *function* domain. As an addition to the ongoing discussing about the contribution of questions 15 and 18 to the *function* domain, an item response theory model could help in determining the value of each question and further refinement of the SRS-22r questionnaire. This model could take into account that not all questions are equally difficult and might correlate with multiple domains, but a sample size of more than 100 respondents is required.[276]

CONCLUSION

The Dutch SRS-22r has the properties needed for measurement of health-related quality of life of AIS patients in the Netherlands. Considering the fact that this is a cross-sectional study, the SRS-22r could be used for the longitudinal follow-up of AIS patients after conservative or invasive surgical treatment. For future research aiming at clinical outcome after treatment of AIS, we recommend the implementation of the Dutch SRS-22r as it could be of clinical importance. While radiographic measures can provide a physician detailed information about the three-dimensional morphology of the spine, self-reported, health-related quality of life measures can provide information about the well-being and performance of the patients in daily life.

Chapter 12

Summary, Answers to the Questions and General Discussion

In the introduction of this thesis (**chapter 1**), the unique features of the upright human spine and clinical characteristics of idiopathic scoliosis were outlined and the research aims described. For further exploration of the role of intrinsic factors in human spinal upright biomechanics in the etio-pathogenesis of adolescent idiopathic scoliosis (AIS) a literature study, multiple diagnostic imaging studies, a biomechanical and a clinical study were performed. The major outcomes of the different studies will be outlined and discussed in the spectrum of development from normal spinal anatomy to three-dimensional spinal deformity in AIS.

DIFFERENT PERSPECTIVES ON THE ETIO-PATHOGENESIS OF AIS

In more than a century of dedicated research into its etio-pathogenesis, many attempts have been made to understand the exact causation of AIS. Now, the amount of causal theories is overwhelming and the etiology of AIS is called 'multi-factorial'.[2, 65]

Since all neuromuscular disorders that act on the growing body inevitably lead to the development of scoliosis, from the beginning it has been inferred that idiopathic scoliosis is the result of a *forme fruste* of neuromuscular disease. This has started in the 1940s with the suggestion that a latent form of poliomyelitis would play a role.[103] Vaccination for poliomyelitis, however, has definitely defeated the disease, but not the occurrence of AIS. Modern day imaging has led to theories that brain stem or spinal cord dysfunction, such as syringomyelia or Chiari type I malformation, may be the cause of subtle muscle imbalance and lead to AIS.[277, 278] Many patients with AIS, however, function very well, often also athletically, up to the moment that they reach puberty and develop a curvature of the spine. After cessation of growth they often do not manifest any other abnormality than their spinal deformity, and certainly no neurologic disability. The drive for understanding the cause of AIS has led to an enormous number of studies on subclinical neuromuscular function of AIS patients and postulation of multiple etiological theories on different mechanisms that influence spinal balance: for example, brain asymmetry, cerebellar morphometry, asymmetrical or impaired proprioception or impaired paravertebral muscle strength.[77, 279-282] Also, many non-neurologic extrinsic factors that potentially lead to AIS have been studied and hypotheses have been postulated for metabolic, endocrine and genetic causal pathways.[66, 204, 283-285]

What abnormalities pre-exist in AIS patients as compared to healthy adolescents, and could these play an extrinsic role in the etio-pathogenesis?

In **chapter 2**, a comprehensive systematic review of the literature was performed in order to give as complete an overview as possible of the concomitant abnormalities that may be relevant for understanding possible etiological pathways of AIS. In this study it was found that a great number of abnormalities that are associated with AIS have been described in the literature, and have been linked to the different etiological hypotheses of AIS.[2] Strong evidence, however, is lacking for a consistent pattern of occurrence of AIS and any given abnormality. Based on the results of our systematic review in chapter 2, the relevance of extrinsic abnormalities in AIS patients appears to be very limited. Unfortunately, as of yet, there are no longitudinal data on abnormalities in AIS patients before the spine started to grow crooked. Due to lack of longitudinal studies and lack of strong evidence for occurrence of any extra-spinal abnormality after the onset of the disease, it seems that the development of scoliosis is the growing spine's pre-conditioned, intrinsic response to any impairment that disturbs the delicate human spino-pelvic balance during growth.

THE ROLE OF POSTERIORLY DIRECTED SHEAR LOADS IN THE ETIO-PATHOGENESIS

Despite the similarities in spinal architecture between species, biomechanical loading can differ greatly, depending on position in space as related to gravity.[11, 136, 286, 287] All spines in nature are predominantly subject to axially compressive as well as ventrally directed shear loads, and its basic anatomy with broad vertebral endplates, discs, posteriorly located facets and processus for muscle and ligament attachment makes it well suited to counteract these loads. The way the human, fully upright spine is biomechanically loaded, however, is a unique feature of the human species, and differs significantly, also from other bipedal mammalians.[5, 6, 8] The upright human spino-pelvic complex is adapted for habitual locomotion by a secondary lordosis that already starts in the pelvis. As a result, certain areas of the thoracic and lumbar human spine are posteriorly inclined in the sagittal plane. In contrast to all other species, these specific spinal segments in the human spine are affected by posteriorly directed shear (figure 1).[22]

Idiopathic scoliosis is also related exclusively to humans and has not been observed in any other mammalian.[9, 288] In 2005, Castelein et al. postulated a hypothesis that these posteriorly directed shear forces, in combination with pre-existent rotation play a decisive role in the etio-pathogenesis of AIS.[5] In the beginning of this research line, Kouwenhoven et al. showed in an *ex vivo* model that posteriorly directed shear loads lead to a decrease in rotational stiffness of spinal segments since no anatomical structure is able to counteract these loads.[6] The human spine, therefore, is a rotationally less stable construct than any other spine in nature (figure 2). The area of the normal growing spine, that is subject to this unfavourable loading, has so far been poorly defined. In 2009, Janssen et al. demonstrated the variance in the amount of posteriorly directed shear loads,

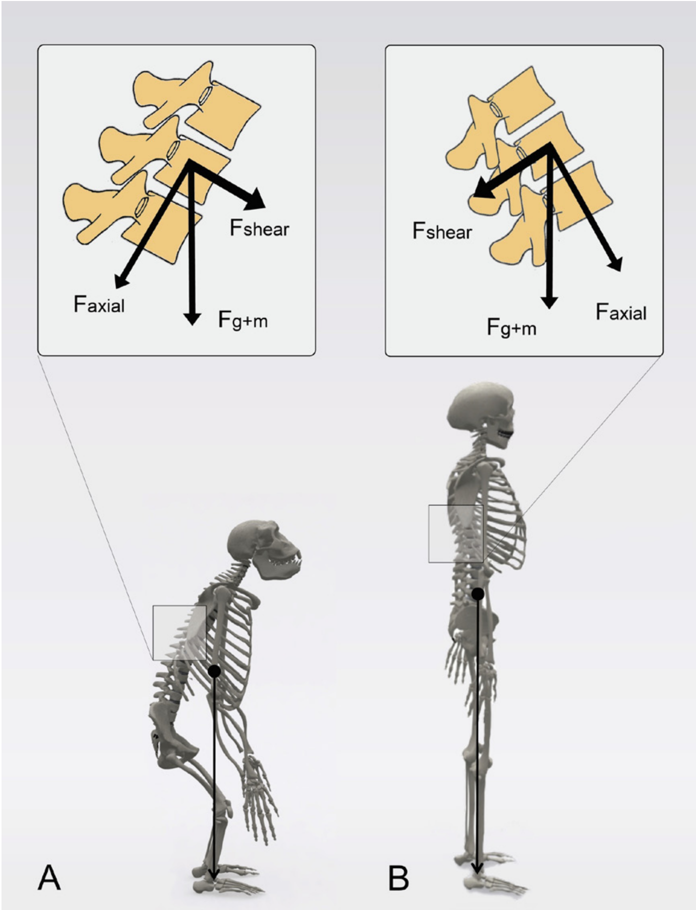

Figure 1. From the sum of gravity and muscle force (F_{g+m}) an axial compression (F_{axial}) and anterior or posterior shear component (F_{shear}) can be composed. Anteriorly inclined vertebra are affected by anteriorly directed shear loads whereas posteriorly inclined vertebra are affected by posteriorly directed shear loads. (*Data compiled from Janssen et al.*[26])

and the area on which they are active, in asymptomatic young adults by measurement of the posterior inclination of the spine on standardized, low dose biplanar radiographs of the spine.[7] It was observed that individual vertebrae in different spinal regions are more posteriorly inclined in females than in males and that the posteriorly inclined segments of the nonscoliotic spines correspond to the rotated segments in AIS. In addition to the concept of posteriorly directed shear forces that facilitate rotation of the vertebrae, it was hypothesized that once rotation occurs, it logically follows an already built in rotation, that is pre-existent in the spine.[5, 28] In multiple studies, Kouwenhoven et al. and Janssen et al. have demonstrated both in humans and quadrupeds, the existence of a rotational pattern of the normal, nonscoliotic spine and that this pattern, although

Figure 2. A metaphoric illustration of decreased rotational stability in the posteriorly inclined area of the spine, according to the etio-pathogenic concept.

smaller in magnitude, corresponds to the direction of rotation observed in AIS.[25-27] In addition, the pre-existent rotational pattern of the human spine was related to organ anatomy and body position, and not to handedness.[24, 26]

For better understanding the factors that play a role in the etio-pathogenesis of AIS, in the first part of this thesis, the unique features of upright spino-pelvic alignment and the role of posteriorly directed shear loads, rotational stability and pre-existent rotation, were explored.

THE CONSEQUENCES OF SPINO-PELVIC MORPHOLOGY OF THE NONSCOLIOTIC UPRIGHT HUMAN SPINE

What is the natural development of sagittal spino-pelvic alignment during the adolescent growth spurt?

It has already been known for decades that pediatric spinal deformities have a well-known age-related preference and gender-related distribution.[30, 63, 107, 157] For example, AIS develops most frequently in girls around the adolescent growth spurt, Scheuermann's kyphosis predominantly in boys around the same phase, and infantile idiopathic scoliosis in boys around the infantile growth spurt. The aim of the study presented in **chapter 3** was to characterize sagittal spino-pelvic alignment and the amount of posteriorly directed shear loads in adolescent girls around peak height velocity and to compare that to the alignment before and after the growth spurt as well as to boys in the same phases of adolescent growth. For this dual-center study, most children were referred by school nurses and underwent radiographic screening for scoliosis, but only children without spinal pathology were included in the study. Moreover, for mature cases it was verified that they, even at the end of the growth spurt, had not developed scoliosis. After applying all exclusion criteria, sagittal spino-pelvic alignment was analyzed on standardized lateral radiographs of 156 non-scoliotic children between 7 and 18 years old. Based on the well documented criteria as presented by Dimeglio on skeletal maturity and timing of the peak of the growth spurt, the subjects were classified into three cohorts based on the closure of the triradiate cartilage as well as Risser's stage: 73 children *before*, 38 *at* and 45 *after* the peak of pubertal growth.[122, 123] The results showed that the thoracic kyphosis, pelvic tilt and pelvic incidence increase during growth and that before and at the peak of the growth spurt, a greater number of vertebrae are more posteriorly inclined as compared to after the growth spurt. Moreover, the spines of girls at the peak of the growth spurt showed more posterior inclination and a smaller thoracic kyphosis as compared to boys. This implies that in girls around the peak of the growth spurt the spine is subject to greater posteriorly directed shear loads, and thus shows less resistance to rotation. This can explain why AIS - under still undetermined circumstances during growth - occurs more in girls than in boys and the incidence of Scheuermann's kyphosis is greater in adolescent boys.

What is the influence of growth and aging on sagittal pelvic morphology?

In the course of human evolution, development of a lordosis between the ischium and ilium allowed for ambulation in a fully upright position, with the body's center of gravity directly above the pelvis, maintaining full extension of the hips and knees. It is important to realize that this posture is essentially different from all other vertebrates, including man's closest relatives, the Bonobo's. In the field of anthropology, it is well-accepted that this 'pelvic lordosis' led to the double-S-shape of the upright human spine, including a more horizontal position of the sacral bone within the pelvic ring and, consequently, the lumbar lordosis.[10, 14, 15, 60, 135, 148, 151, 289] Even in human's earliest ancestor (the species *Australopithecus afarensis*, also known as "Lucy", which was discovered in Ethiopia in 1974 and supposedly walked upright 3.2 million years ago, this lordosis can be found (figure 3).[12, 148] As a result of this unique configuration in space of the human spino-pelvic complex, unique biomechanical forces - with relevance for a number of spinal conditions - were introduced. Also from studies that used the well-known, clinical parameter

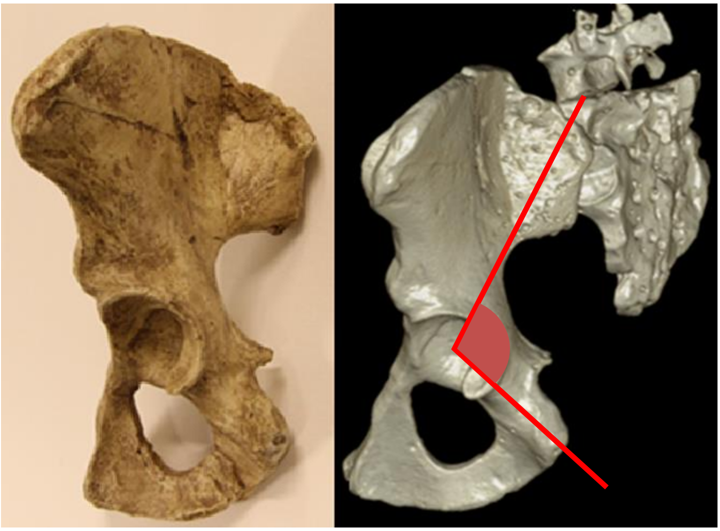

Figure 3. A photograph and three-dimensional reconstruction of a computed tomographic scan of Lucy's pelvis (*Australopithecus afarensis*). The pelvic lordosis (i.e. ischio-iliac angulation) is indicated in *red*.

"pelvic incidence", we know that the pelvis is an important determinant of global sagittal alignment of the spine.[16-18] In **chapter 4** we introduce a novel pelvic parameter that describes the relationship between the changes that were observed in human evolution and human sagittal spino-pelvic alignment: the ischio-iliac angle or pelvic lordosis. The aim of the study presented in chapter 4 was to quantify, for the first time in literature, the development of the ischio-iliac lordosis in the normal growing and adult pelvis, and to evaluate its correlation with the better known and widely used pelvic incidence. For this study, a semi-automatic analysis was performed on 499 CT-scans of the pelvis in asymptomatic children (n=189) and adults (n=310), using previously validated image processing techniques (**appendix 1**). In this observational study, a wide variation of the ischio-iliac angle and pelvic incidence was found. Interestingly, a significant correlation between the ischio-iliac angle en pelvic incidence was demonstrated and it was found that both parameters increase during pediatric growth and become constant after adolescence. Despite the fact that no positional parameters were assessed in this study due to the supine position of the subjects in the CT scanner, these results imply that the ischio-iliac angle is in harmonious continuity with the lumbar lordosis; given the relationship between the pelvic incidence and lumbar lordosis, it forms the basis for human upright spinal biomechanics.[16-18] In future studies, the question can be addressed whether the ischio-iliac lordosis can be used as a predictor for the onset or progression of different growth related pathologies of the spine such as AIS, spondylolisthesis, Scheuermann's kyphosis, as well as for degenerative diseases of the spine or hips or low back pain.[68, 114, 155, 290]

What are the pre-existent rotational patterns of the normal pediatric spine?

The most prevalent curve type in AIS is a right convex main thoracic curve with compensatory high-thoracic and (thoraco)lumbar curves to the left.[41] Previously, it was shown that once the spine decompensates into a scoliosis, for whatever reason, the direction of spinal curvature is determined by an already built-in rotational pattern.[25, 291] In contrast to adolescent scoliosis, the main thoracic curve in infantile idiopathic scoliosis rotates and deviates far more often to the left, whereas in juvenile idiopathic scoliosis this pattern is more evenly distributed between right and left.[292] The aim of the study presented in **chapter 5** was to determine whether a distinct pattern of vertebral rotation in the transverse plane exists in the normal, non-scoliotic infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old) human spine. We measured the rotation of each individual vertebra between T2 and T12 on CT scans in 146 asymptomatic children. Repeated measures statistical analysis revealed significant differences in the rotational patterns of the spine between the three age cohorts: At the infantile age the spine was rotated to the left at all thoracic levels, at the juvenile age thoracic vertebra were oriented in the midline. In contrast, at the adolescent age the mid- and low thoracic levels (T6-T12) were significantly rotated to the right side, as has been shown in adults previously as well.[25] Therefore, our analyses of non-scoliotic vertebral columns at different ages shows that transverse plane asymmetry is also a normal feature of the pediatric spine. Furthermore, the different rotational patterns between the infantiles, juveniles and adolescents in this study match the rotation and convexity of the curve as is normally seen in idiopathic scoliosis. Therefore, the hypothesis that the convexity of the curve in idiopathic scoliosis is determined by a pre-existent rotational pattern is supported.[28]

Do the pre-existent rotational patterns of the pediatric spine correspond to asymmetrical closure of the neurocentral junctions?

It has previously been suggested that rotation of the spine in idiopathic scoliosis is the result of asymmetrical closure of the neurocentral junctions (NCJs).[53, 54, 293] From this perspective, active unilateral growth of the right NCJ leads to vertebral rotation to the left. However, this can also be a secondary phenomenon as a *result* of rotation, rather than its *cause*. According to Hueter-Volkmann's law, it can be expected that also axial rotation of a vertebra will secondarily lead to asymmetric pressures on the growth cartilage of the NCJ, subsequently leading to asymmetrical closure patterns of this structure.[172, 173] Axial rotation and NCJ closure, therefore, can be expected to be related, irrespective of the debate whether it is active or passive growth leading to closure of the NCJs. Similar to scoliosis, it can be hypothesized that also the rotational patterns of the nonscoliotic pediatric spine are related to asymmetrical closure of the NCJs. Previously, this relation has not been investigated for asymptomatic children. In **chapter 6**, axial rotation and

NCJ closure was studied in the thoracic and lumbar spine in a total of 199 nonscoliotic children (including the 156 children analyzed in chapter 5) using dedicated segmentation software for measurement of the absolute surface area of the NCJs. It was found that closure of the NCJs starts in the lumbar spine (L1-L3) at 4-5 years of age, followed by the lower lumbar (L4-L5) and high-thoracic spine, and at last in the mid and low thoracic spine at 8-9 years of age. In addition, in the thoracic spine at the infantile age, the right NCJ was predominantly larger, whereas at the juvenile age the left NCJ was larger. At the adolescent age, most levels (90%) were already closed. Taking the result of chapter 5 and 6 into account, the pattern of closure of the NCJs corresponds to the pre-existent rotational patterns of the pediatric spine and the convexity of the curve in idiopathic scoliosis. The role of active growth of the NCJs in the onset and progression of axial rotation in AIS, however, must be limited since the neurocentral junctions are already largely closed, and thus inactive, at the adolescent age. Pre-existent rotational pattern and the asymmetrical closure pattern of the NCJs, however determine the convexity of the curve once scoliosis develops.

MECHANISMS IN THE DEVELOPMENT OF AIS

The second part of this thesis aimed at further exploration of the biomechanical mechanisms in progression of AIS.

What is the difference in sagittal spino-pelvic alignment between thoracic and lumbar AIS at an early stage?

Previously, the concept has been explained in which the human spine is, in a rotational sense, a much less stable construct than any other spine in nature: Rotational stiffness of spinal segments that are posteriorly inclined is decreased by posteriorly directed shear loads and these posteriorly inclined segments correspond to the rotated segments as seen in AIS.[5, 8] This concept differs significantly from for example the concept of Dickson et al. in which idiopathic scoliosis starts as a thoracic lordosis, whereas in this concept lordosis is the consequence of rotation, not the cause.[22, 30, 37] According to our concept, it can be inferred that the area of the spine in which a rotational deformity has a chance to develop, is based on differences in sagittal spino-pelvic alignment before the onset of the deformity. The hypothesis that thoracic AIS develops in a different sagittal profile as compared to (thoraco)lumbar AIS was tested in an international dual-center study as presented in **chapter 7**. To test the causal relation of the sagittal spinal profile and development of AIS, it would be ideal to have longitudinal data on the sagittal profile of the spine at the juvenile age, before the onset of the deformity, because the sagittal spinal contour is affected by the spinal deformity itself. However, since it seems practically and ethically very difficult to perform such a study, using radiographs in asymptomatic children, we performed a study with a 'second best' design to test the hypothesis: From a multicenter database of almost 1400 AIS patients, all lateral radiographs were reviewed of children with an established, but still very small (Cobb angle smaller than 20 degrees) thoracic (Lenke 1 and 2, n=128) and (thoraco)lumbar AIS (Lenke 5, n=64). We also collected radiographs of nonscoliotic controls. Systematic analysis of the sagittal profile and exact inclination of each individual vertebra – the same method as used in chapter 3 and a previous study[23] – revealed that already at this very early stage, the thoracic kyphosis and posterior inclination of thoracic AIS differs significantly from (thoraco)lumbar AIS as well as from controls. More precise, in thoracic scoliosis most thoracic vertebra were more backwardly inclined as compared to (thoraco)lumbar scoliosis and vice versa. Our setup was not unique. Other researchers have also investigated the differences in sagittal spino-pelvic alignment between different types of AIS, but mostly only analyzed the global parameters thoracic kyphosis and lumbar lordosis without taking the consequences of the biomechanical loading of the spine into account.[116, 146, 177] Analogous to our previous studies, these results demonstrate that the posteriorly inclined segment corresponds to the rotated segments in different types of AIS. This difference in sagittal profile was shown to already exist at a very early stage of the development of the rotation and the curvature, and thus can be postulated to play a role in the pathogenesis of the different curve types. This is in accordance with the previously postulated etiological concept.

What is the true 3-D morphology of AIS?

Modern day surgical techniques aim at restoring normal anatomy as closely as possible. Understanding the true 3-D morphology of the spine in AIS is important both theoretically for understanding the disorder, and for daily practice, since both considerations require accurate knowledge of the exact nature of the disorder.

Eighteenth and nineteenth century anatomists already described the 3-D morphology of scoliotic curvatures in great detail in *post-mortem* studies.[1, 33, 206] The importance of the sagittal plane was already well appreciated at that time, as becomes manifest from the statement of Meyer in 1866: "*Aus den angegebenen Grunden findet man: mit jeder Skoliose der Brustgegend verbunden einen entsprechenden Grad der (relativen oder absoluten) Lordose*" (in English: Based on the abovementioned findings, in each thoracic scoliosis there is a corresponding degree of (relative or absolute) lordosis).[33] With the advent of radiography, unfortunately scoliosis gradually became regarded as a coronal plane deformity, until a number of authors re-emphasized the importance of the sagittal plane.[34, 35, 37, 38, 294] Ultimately, this has led to the assumption that idiopathic scoliosis may be a problem of generalized anterior overgrowth of the whole spine, or a discrepancy of growth of the spinal cord as compared to growth of the vertebrae.[56, 57, 186, 208, 295] Although the 3-D aspect of AIS has been studied for over a century and has been given much attention in recent years in the literature, the true 3-D morphology, and especially the sagittal deformation, of the different areas of the scoliotic spine has not been described in detail before.

Since 2011, at the Chinese University of Hong Kong, all AIS cases to be operated, have undergone high-resolution computed tomographic imaging of the spine preoperatively for navigation purposes. This dataset as well as a dataset of CT scans of normal children (taken for unrelated purposes as trauma, pulmonary disease, etcetera) were used for the investigation presented in **chapter 8**. The scans were analyzed using special software to calculate 'endplate-vectors' and describe the 3-D deformation of different regions of the spine in AIS patients in the coronal, transverse and true sagittal plane in great detail. Interestingly, quantitative description of the 3-D morphology of AIS revealed that (1) the 3-D development of AIS curves follows a rather uniform pattern with coupling of the different aspects of the deformity in all three planes and that (2) all AIS curves, structural as well as nonstructural, primary as well as compensatory, thoracic as well as (thoraco) lumbar, were characterized by greater anterior length measured from Cobb end vertebra to Cobb end vertebra. The junctional segments in-between the curves were more or less straight.

Where is the 3-D deformity in AIS localized, in the discs or vertebral bodies?

In two-dimensional radiographic studies on AIS, contradictory findings have been reported on the individual contribution of the vertebral bodies as compared to the discs to the coronal deformity.[194-203] Furthermore, active growth phenomena and disorders of bone metabolism have been suggested to play an etiological role. In **chapter 9**, we address the important question in which anatomical structure and in which plane the deformity starts in AIS. In this study, the individual contributions of the discs and vertebral bodies to the true three-dimensional deformity of the spine in AIS were analyzed. The same series of high-resolution CT-scans and software as used for the study presented in chapter 8 were evaluated. For this study, segmental parameters were determined for each individual disc (total n=924) and vertebra (total n=1078) between T4 and L5. In contrast to previous studies, in scoliosis the intervertebral discs were at least three times more deformed in the coronal, true transverse and true sagittal plane than the vertebral bodies.[199, 201] Anterior-posterior and coronal wedging was more pronounced at the apices of the curves, whereas mechanical torsion was found in all regions of the spine. Conclusions from this and the previous study (**chapter 8**) are that excess of anterior length is not a global, but rather a regional phenomenon, and that, since the deformity is much more in the disc than in the bone, it seems more of a passive phenomenon than an active growth process.

IMPLICATIONS FOR CLINICIANS TREATING AIS PATIENTS IN THE NETHERLANDS

The primary goal of scoliosis surgery has always been to prevent progression, provide a balanced spine in the coronal and sagittal plane, fuse as few vertebrae as possible and avoid complications. There is evidence, however, that recreating as normal as possible anatomy, is beneficial to the remaining, unfused areas of the spine.[296-298] Even with modern day surgical techniques, it remains difficult, however, to really recreate the normal shape of the spine and avoid problems like thoracic hypokyphosis and junctional decompensation (figure 4). For corrective scoliosis surgery it is essential to have a thorough understanding of the deformity of the spine in all three dimensions, and the obstacles to reduction. For assessment of *in vivo* 3-D morphology, high-resolution computed tomographic scans are considered as the gold standard technique, but have the disadvantage that they can so far only be acquired in the prone position.[180] For practical

Figure 4. Proximal junctional kyphosis in *red* in a 16-year-old girl at two years of posterior scoliosis spondylodesis for adolescent idiopathic scoliosis.

purposes, in **chapter 8**, we demonstrate how the true 3-D morphology can be predicted based on measurements on conventional 2-D radiographs.

What effect do multilevel posterior releases have on spinal mobility?

In chapter 8, it was demonstrated that the anterior part of the spine in AIS is relatively too long from upper Cobb end vertebra to lower Cobb end vertebra, as compared to normal anatomy. There are two possible approaches to this excess of anterior length; posterior lengthening or anterior shortening. Posterior techniques have become the mainstay of treatment of scoliosis, based on our anatomical analysis it can be proposed that anterior techniques should not be abandoned and may indeed have to undergo a revival. Focusing on the posterior approach, it is not clear how much posterior ligament releases should be performed in order to lengthen the posterior side of the spine and restore a normal sagittal profile. In the biomechanical study presented in **chapter 10**, we tested the effectiveness of different, step-wise posterior ligament releases, that are commonly used in surgical practice for lengthening the posterior side of the thoracic spine. In an *ex vivo* model that was previously validated, range of motion in the three dimensions was tested in nonscoliotic thoracic specimens after subsequent posterior releases, including a full Ponte osteotomy.[58] It was found that removal of posterior ligaments allows for more flexibility, and thus better correction, in the sagittal, and in the coronal and transverse plane. It was demonstrated how much flexion can be achieved by each step of the posterior release, this can be used as a surgical guideline. Superior facetectomy, as is performed in the widely used Ponte osteotomy for release of the spine, had no clinically relevant additive effect (0.1 degrees extra flexion per segment) on spinal mobility in the sagittal plane after subsequent release of the interspinous ligaments, ligamentum flavum and the inferior facet. When the results of chapter 8 and 10 are combined, adding lengthening procedures posteriorly to obtain an approximate additional 8% posterior length from Cobb to Cobb is an option to obtain normal thoracic kyphosis.[299] Also, anterior shortening by discectomies or wedge resection is a valid option if maximal correction in all planes is considered desirable.[58, 300]

Can we translate and adapt the revised Scoliosis Research Society 22-item questionnaire for the Netherlands?

Because of the increasing interest, also among Dutch spine surgeons, to measure health-related quality of life in patients with AIS, in **chapter 11**, the revised Scoliosis Research Society 22-item questionnaire was translated into Dutch, adapted for the Netherlands and validated.[59] After this process, it was concluded that the Dutch SRS-22r had the properties needed for the measurement of patient perceived health-related quality of life of AIS patients in the Netherlands. Already, the questionnaire gained acceptance in different parts of the Netherlands and is used in clinical trials for longitudinal follow-up AIS patients in order to establish the effects of modern conservative and invasive treatments of these patients.

FINAL CONCLUSIONS AND FUTURE PERSPECTIVES

Before this thesis, it was already known that under certain circumstances (when there is imbalance between the acting force and its compensating mechanism), an excess of axial compression of the adolescent spine causes a deformity known as Scheuermann's kyphosis.[107] Similarly, excess of anteriorly directed shear loads can result in spondylolisthesis.[68, 290] In this thesis, the impact on spino-pelvic balance of a third force, that uniquely acts on certain segments of the upright human spine, was studied: posteriorly directed shear forces.

In summary, in this thesis evidence from multiple cross-sectional imaging studies is provided that supports the hypothesis that AIS is the result of decreased rotational stiffness of the spine due to an excess of posteriorly directed shear loads. Our studies also demonstrated that once the spine decompensates into an idiopathic scoliosis it will follow the pre-existent rotational pattern of the nonscoliotic spine. This spinal deformation ultimately leads to rotated lordoses around the apices of the curvatures and has significant impact on quality of life. We can conclude that AIS has an intrinsic biomechanical basis: An imbalance between the biomechanical loading of the upright human spine (i.e. posteriorly directed shear loading) on the one hand and the body's compensating mechanisms on the other.[5]

For further clarification of the etio-pathogenesis of AIS and the role of posteriorly directed shear forces, there is a need for a large-scale investigation into the changes of normal sagittal spino-pelvic alignment in which children at risk for scoliosis should be longitudinally followed during the adolescent growth spurt until adulthood. Modern low-dose three-dimensional imaging techniques or digital postural measurements might help to withdraw the ethical concerns in the case of a longitudinal radiographic study in asymptomatic children.[132, 180] In addition, populations that are at higher risk for development of AIS, such as family members of AIS patients or 22q11 deletion syndrome could help to maximize the efficacy of a longitudinal study.[157, 301] Then, it can be verified which sagittal spinal configuration predisposes a child to AIS, Scheuermann's kyphosis or normal development into the adult spinal configuration and whether progression can be predicted accurately.

In addition, the question remains: "What underlying mechanisms and structures influence rotational stability of the spine and predisposes the spine of otherwise healthy children to decompensate into a rotational deformity, while the spine of other children stays unaffected?" In one of our studies, it was found that the geometry of the intervertebral disc is most affected in AIS as compared to the vertebral bodies. Moreover, this structure possibly plays a key role in the rotational stability of the pediatric and adult spine. From our perspective, as a first step to answer this question, factors that influence the rotational stability of the intervertebral discs should be elucidated. Modern, non-ionizing, imaging techniques, such as T1ρ or T2-mapping magnetic resonance imaging, are considered to be helpful in this matter.[302]

As research continues on the pathogenesis of AIS, it can be expected that the biological and mechanical mechanisms in the pathogenesis of AIS can be revealed, and possible risk factors for the development and progression of AIS can be identified at an early stage, when less invasive treatment is still an opportunity. This is needed in order to develop adequate causal treatment, as until now, treatment of AIS is mainly focussed on treating the secondary symptoms.

Appendix 1

Computerized Determination of the Ischio-Iliac Angle from CT Images of the Pelvis

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A supplement to chapter 4: Evolution of the Ischio-Iliac Lordosis during Natural Growth and Its Relation With the Pelvic Incidence. European Spine Journal, 2014 ul;23(7):1433-41. doi: 10.1007/s00586-014-3358-z.

INTRODUCTION

The computerized method for the determination of ischio-iliac angle from computed tomography (CT) images of the pelvis exploits the image intensity appearance of CT images and the anatomical information in the form of the shape of the observed objects of interest (i.e. sacrum, femoral heads, ischium) in three dimensions (3-D). The applied algorithms were implemented in the C++ programming language and can be run on any standard personal computer. The method consists of the following parts:

- user initialization,
- computerized determination of the exact centers and size of femoral heads in 3-D,
- computerized determination of the exact center and inclination of the sacral end-plate in 3-D,
- computerized determination of the left and right ischial axis in 3-D, and
- computation of the ischio-iliac angle.

USER INITIALIZATION

For a given 3-D CT image of the pelvic and lumbar spinal area of the observed subject (at least L5 vertebral body visible), the user manually determined the approximate center of the left femoral head, right femoral head and L5 vertebral body by navigating through sagittal, coronal and axial cross-sections (Figure 1). In is important to note that these anatomical structures can be easily identified in 3-D with basic anatomical knowledge. Moreover, the resulting three points were not required to be at the exact centers of these anatomical structures but served to initialize the computerized method by defining the locations of the volumes of interest (VOIs) in the 3-D image.

COMPUTERIZED DETERMINATION OF THE EXACT CENTERS AND SIZE OF FEMORAL HEADS IN 3-D

The determination of the exact centers and size of the femoral heads in 3-D was performed independently for the left and right femoral head. For each femoral head, a VOI of size 70 × 70 × 70 mm and centered in the corresponding manually defined initialization point (i.e. the approximate center of the femoral head) was first extracted. To determine the exact center of the femoral head, we exploited the geometrical properties of image intensity vectors, which were computed using Sobel gradient operator. Namely, image intensity gradient vectors are orthogonal to the edges in the image, and their magnitude is proportional to the edge strength, i.e. the magnitude is in the case of CT

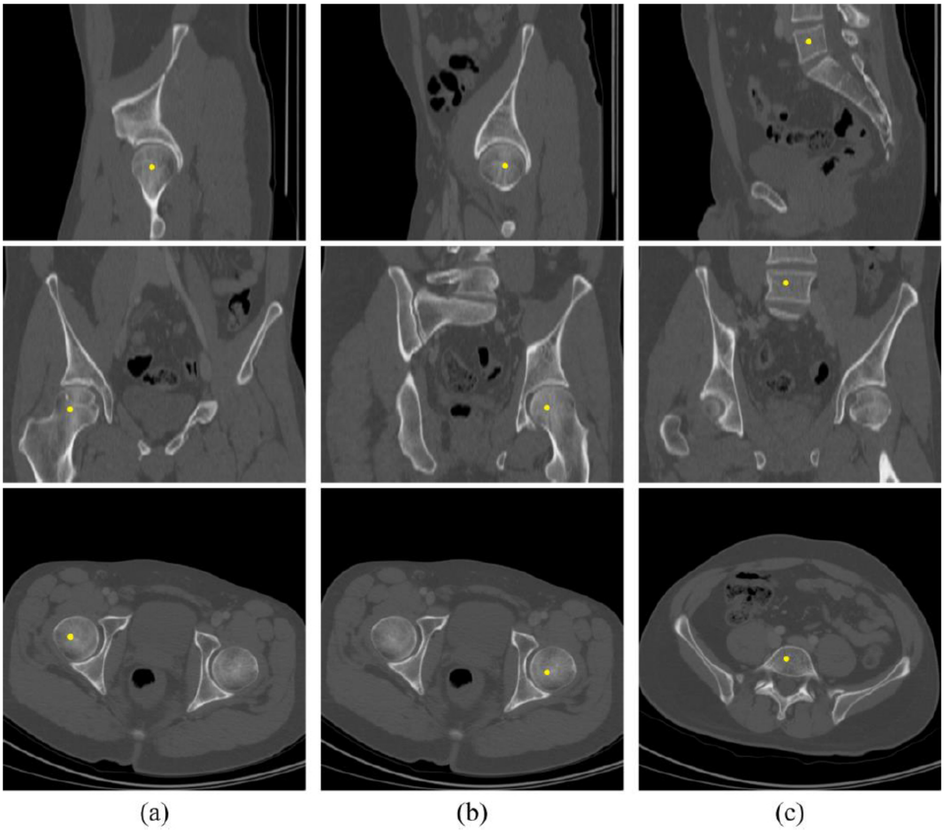

Figure 1. The manually defined approximate centers of (*a*) the left femoral head, (*b*) the right femoral head and (*c*) the L5 vertebral body, which served to initialize the computerized method for the determination of ischio-iliac angle, shown in corresponding sagittal (*top*), coronal (*middle*) and axial (*bottom*) CT cross-sections of a selected subject.

images therefore the largest on the edges of bone structures. At each point in the VOI, a line in the direction of the image intensity gradient vector at that point was constructed. By superimposing the lines obtained from every point, a 3-D accumulator image of the VOI was obtained, and its values represented the probabilities where these lines most often intersected. As the femoral head is a relatively spherical structure, lines most often intersected in the geometrical center of the femoral head, which was identified as the location of the maximal value of the 3-D accumulator image. Once the center of the femoral head was determined, its size was obtained by finding the best fit sphere that maximized image intensities within the sphere and the magnitude of image intensity gradient vectors on the surface of the sphere (Figure 2).

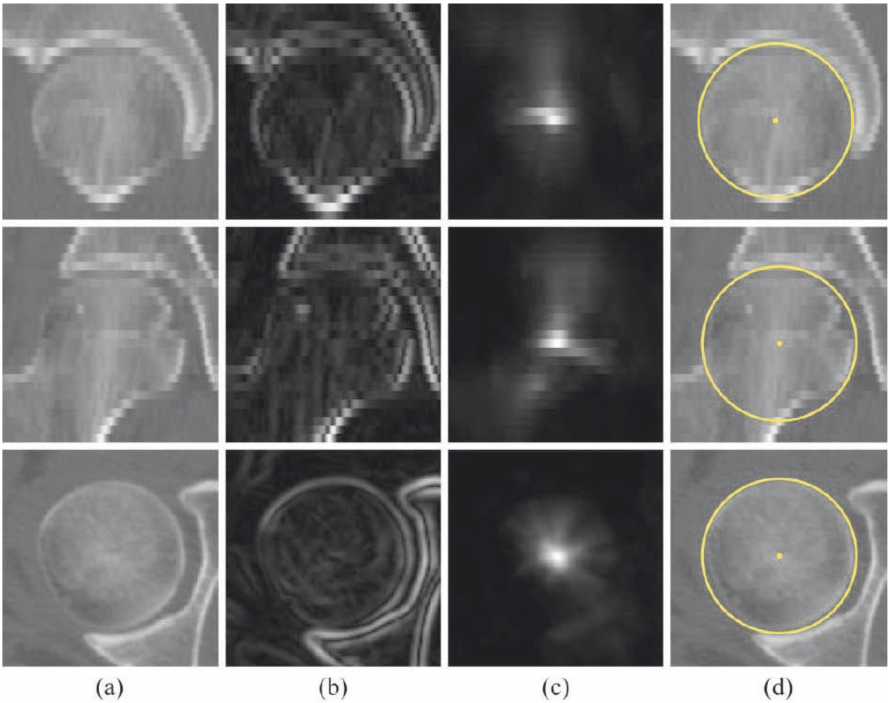

Figure 2. The determination of the exact center and size of the left femoral head in 3-D, shown in its mid-sagittal (*top*), mid-coronal (*middle*) and mid-axial (*bottom*) CT cross-section as (*a*) original images, (*b*) magnitudes of image intensity gradient vectors, (*c*) accumulator images of lines in the direction of image intensity gradient vectors, and (*d*) original images with the obtained center and size of the femoral head.

COMPUTERIZED DETERMINATION OF THE EXACT CENTER AND INCLINATION OF THE SACRAL ENDPLATE IN 3-D

The determination of the exact center and inclination of the sacral endplate in 3-D was performed by first extracting a VOI of size 100 × 100 × 100 mm that was centered in the manually defined initialization point (i.e. the approximate center of the L5 vertebral body). Next, the surface of the sacral endplate was identified as the first bone structure below the L5 vertebral body by observing image intensities in the CT image and the corresponding image intensity gradient vectors. From the center of the VOI (i.e. from the initialization point), rays were projected at different angles in the caudal direction, and image intensities were computed along each ray. As, in the case of CT images, the ray with the maximal sum of image intensities is oriented towards the largest bone structure, it was selected to represent the direction of the sacrum. The point on the surface of the sacral endplate was identified from the largest image intensity gradient vector (oriented outwards of bone structures) along the selected ray. The exact center and inclination of the sacral endplate were then found in an optimization procedure. An elliptical plane that was centered in the currently identified point on the surface of the sacral endplate was determined by optimizing the sagittal and coronal inclination of the plane according to the largest sum of image intensities within the plane, which resulted in the inclination of the sacral endplate. Then, within the resulting plane, a new center point was defined as the current center of the sacral endplate by searching for image intensities and corresponding image intensity gradient vectors representing the edges of the sacrum in the left and right, and in the anterior and posterior direction of the center point. The procedure for defining the best fit plane and the best located center point of the sacral endplate was repeated until a relatively small difference in results was detected between two consecutive iterations (Figure 3).

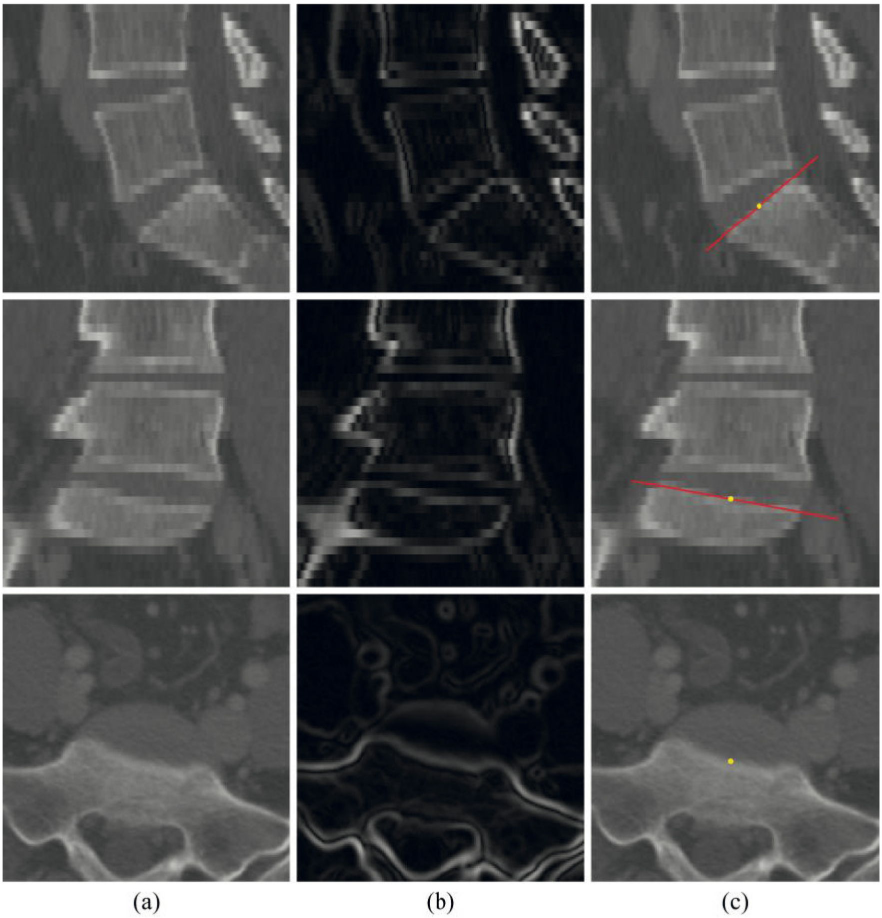

Figure 3. The determination of the exact center and inclination of the sacral endplate in 3-D, shown in its mid-sagittal (*top*), mid-coronal (*middle*) and mid-axial (*bottom*) CT cross-section as (*a*) original images, (*b*) magnitudes of image intensity gradient vectors, and (*c*) original images with the obtained center and inclination of the sacral endplate.

COMPUTERIZED DETERMINATION OF THE LEFT AND RIGHT ISCHIAL AXIS IN 3-D

From the identified center of each (left or right) femoral head, the superior endpoint of the corresponding ischial axis was initialized along a line at 30° above the hip axis (i.e. the line connecting the centers of both femoral heads) and 15 mm from the edge of the femoral head (represented by the sphere determining its size) into the pelvis. This point was then used to initialize a truncated elliptical cone (i.e. a conical cylinder) of length 100 mm and with equal initial superior and inferior radii of 10 mm. The inclination and size of this cone were then optimized according to image intensities and image intensity gradient vectors captured within the cone. It is important to note that the aim was not to segment each ischium, but to find its inclination represented by its axis. As a result, the axial location of the superior part of the cone, as well as the length of the cone, were fixed, while its inclination in 3-D, and its superior and inferior radii were optimized to best fit each ischium in the CT image. Moreover, the optimization was performed simultaneously for the left and right ischium, as the sagittal inclination of both cones measured from the hip axis was represented by one angle to obtain a single inclination value, used for the computation of the ischio-iliac angle (Figure 4).

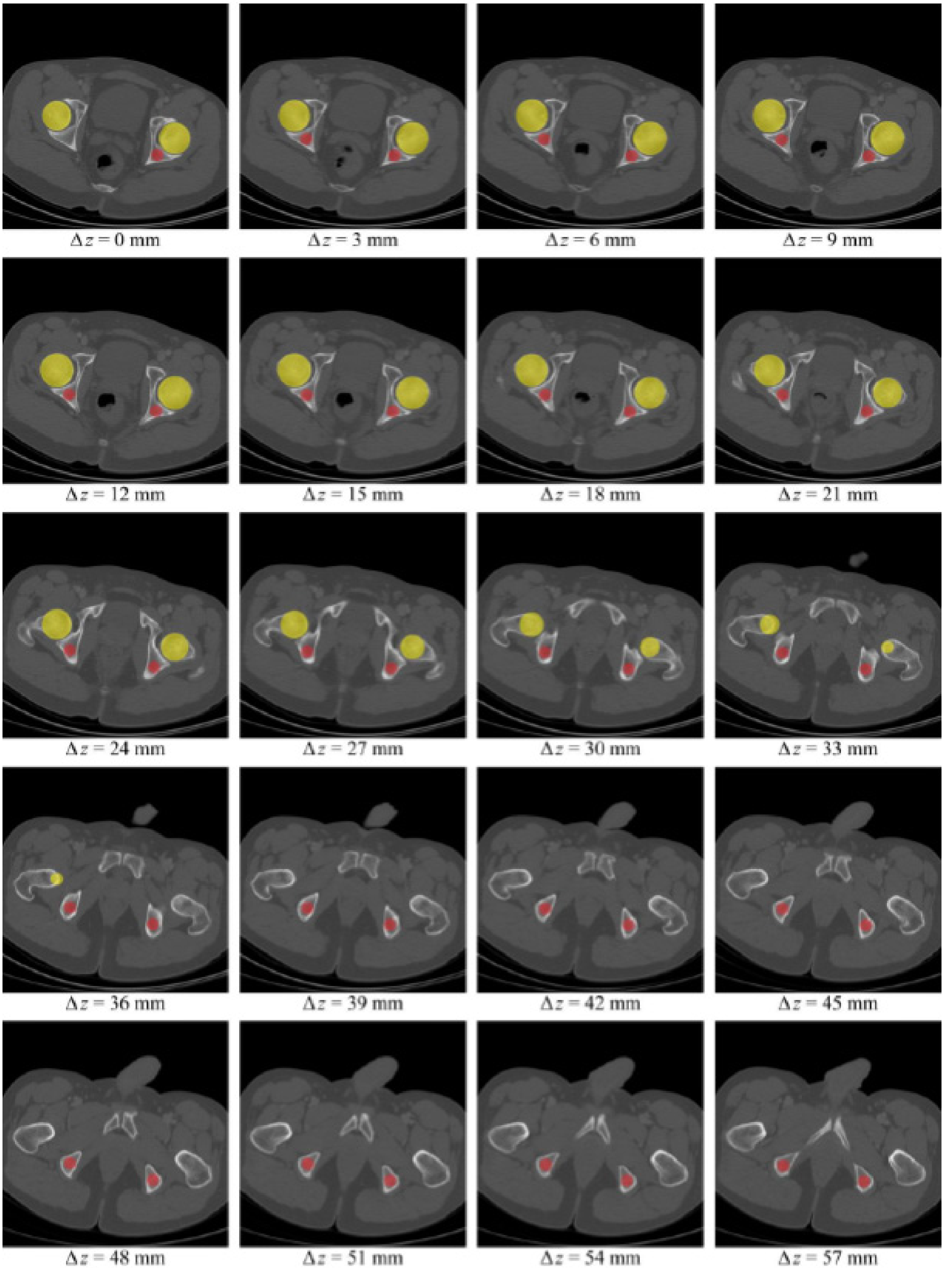

Figure 4. Consecutive axial CT cross-sections (Δz denotes the offset from the first cross-section) with the obtained left and right femoral heads (cross-sections of spheres, in *yellow*), and of the obtained left and right ischia (cross-sections of truncated elliptical cones, in *red*).

COMPUTATION OF THE ISCHIO-ILIAC ANGLE

Before computing the ischio-iliac angle, multiplanar 3-D image reformation was performed to obtain the superposition of the femoral heads in the sagittal view. As a result, the hip axis was observed as a non-inclined line and all anatomical structures were completely in line with the hip axis. Finally, the ischio-iliac angle was automatically calculated in the reformatted sagittal plane as the angle between the line connecting the hip axis (i.e. centers of femoral heads) with the center of the sacral endplate, and the line along the axes of both ischia (Figure 5).

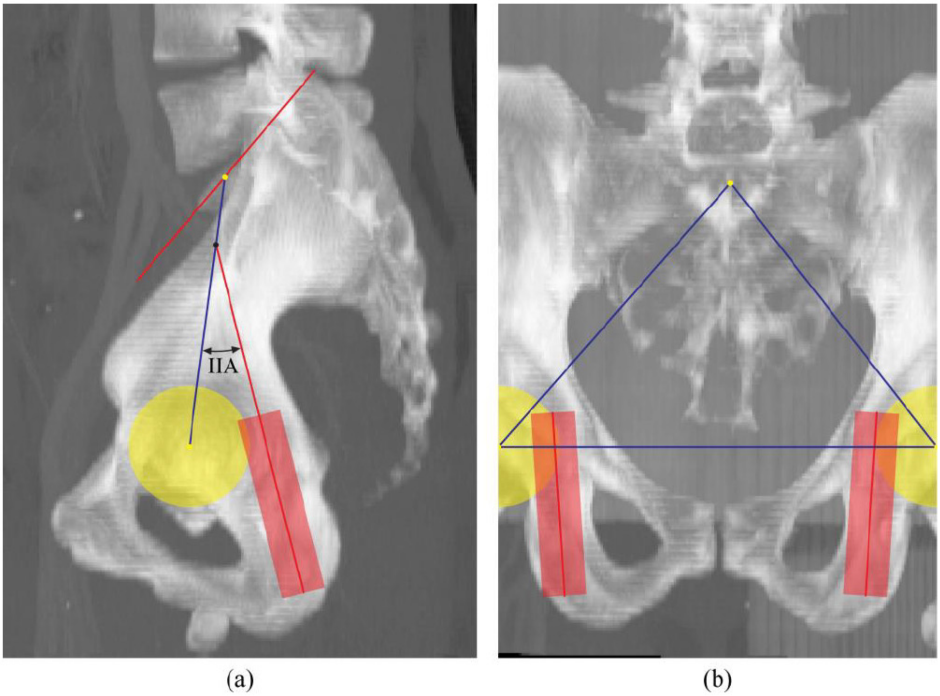

Figure 5. The ischio-iliac angle (IIA) is defined in the reformatted sagittal plane, which is perfectly aligned with the hip axis, as the angle between the line connecting the hip axis and the center of the sacral end-plate (blue lines), and the line along the axes of both ischia (red lines), shown in (*a*) sagittal and (*b*) coronal maximum intensity projection (MIP) images.

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Nederlandse Samenvatting

Scoliose is een driedimensionale (3-D) vervorming van de wervelkolom en romp die primair ontstaat in aanvankelijk volstrekt gezonde kinderen. Het is een klassiek orthopaedisch probleem.[1] De meest voorkomende vorm van scoliose is *idiopathische* scoliose. De term 'idiopathisch' betekent letterlijk dat de aandoening ontstaat uit zichzelf en deze dus niet direct gekoppeld is aan een ander lichamelijk probleem of aan een bepaalde medische voorgeschiedenis. Ondanks jarenlang toegewijd onderzoek naar de etiopathogenese van idiopathische scoliose, is er dusver niet één aanwijsbare oorzaak voor deze aandoening en wordt de etiologie bestempeld als 'multifactorieel'.

Vooralsnog is er geen adequate oorzakelijke behandeling beschikbaar en zijn er geen voorzorgsmaatregelen mogelijk. Tot op heden wordt pas gestart met behandelen als de deformiteit erg uitgesproken is. Dit behelst agressieve conservatieve of chirurgische behandelingen. Naast de gevolgen van de verkromming van de wervelkolom voor de kwaliteit van leven van deze patiënten, zijn scoliosepatiënten ook een aanzienlijke economische belasting voor de maatschappij; Ongeveer 2-3 procent van de populatie is aangedaan, ongeveer zes miljoen mensen in de Verenigde Staten hebben een idiopathische scoliose, het is de deformiteit die huisartsen, kinderartsen en orthopaedisch chirurgen het vaakst tegenkomen en de beschikbare behandelingen zijn zeer kostbaar.[3, 4]

Het is eerder aangetoond dat de wijze waarop mensen volledig rechtop lopen uniek is en een belangrijke rol speelt in het ontstaan en de progressie van idiopathische scoliose.[5-8] Idiopathische scoliose komt alleen bij de mens voor en is nooit geobserveerd bij andere diersoorten.[9] Andere vervormingen van de wervelkolom zijn wel eerder gezien bij andere soorten, maar deze hadden een aanwijsbare iatrogene, post-traumatische, neuromusculaire of congenitale oorzaak. De wijze waarop mensen volledig rechtop staan, alsmede het bipedale voortbewegen, verschilt aanzienlijk van andere viervoetige én tweevoetige gewervelden. Hierdoor is ook de biomechanische belasting van de rechtopstaande wervelkolom, waarbij er een zeer nauwe balans is tussen krachten die inwerken op de wervelkolom en de compensatiemechanismen van het lichaam, een unieke eigenschap van de mens.[5, 7, 8]

OPZET VAN DIT PROEFSCHRIFT

In de introductie van dit proefschrift (**hoofdstuk 1**) zijn de unieke eigenschappen van de rechtopstaande wervelkolom van de mens en klinische kenmerken van idiopathische scoliose uiteengezet en de onderzoeksdoelen beschreven. In het kort, het doel van dit proefschrift is om te bepalen welke intrinsieke factoren in de biomechanica van de rechtopstaande menselijke wervelkolom een rol spelen in de etiologie en pathogenese van adolescente idiopathische scoliose (AIS). Uiteindelijk zal beter inzicht in de ware oorzaak en bijkomende factoren van deze aandoening in de toekomst leiden tot rationelere, minder invasieve en minder kostbare therapieën, alsmede tot voorzorgsmaatregelen.

Het proefschrift is onderverdeeld in twee delen met daarin een literatuurstudie, verschillende beeldvormende studies, een biomechanische en een klinische validatie studie. In deel 1 zal het sagittale profiel van het bekken en de wervelkolom van mensen zonder scoliose in detail worden gekarakteriseerd. Deel 2 richt zich op verdere bestudering van de biomechanische mechanismen in de ontstaanswijze en het verdere beloop van AIS. Tevens zal in dit deel de ware 3-D anatomie van scoliose in detail worden beschreven, zullen de gevolgen voor chirurgische correctie worden besproken en zal een internationale patiënt gerapporteerde vragenlijst worden gevalideerd voor Nederland.

In dit hoofdstuk zal het proefschrift worden samengevat door het uiteenzetten van de voornaamste uitkomsten van de verschillende onderzoeken, het beantwoorden van de onderzoeksvragen en door discussie hiervan in het kader van normale spinale anatomie tot 3-D deformiteit.

VERSCHILLENDE PERSPECTIEVEN OP DE ETIOPATHOGENESE VAN AIS

Gedurende meer dan een eeuw gedegen onderzoek naar de etiopathogenese zijn er vele pogingen gedaan om de exacte oorzaak van AIS te begrijpen. Dusver is het aantal theorieën over de oorzaak overweldigend en wordt de etiologie van AIS bestempeld als multifactorieel.[2, 10]

Omdat alle neuromusculaire ziektes die inwerken op het groeiende lichaam onmiskenbaar leiden tot de ontwikkeling van scoliose, wordt vanaf het begin aangenomen dat idiopathische scoliose het resultaat is van een milde, atypische vorm van een neuromusculaire aandoening. Dit is begonnen in de veertigerjaren met de suggestie dat een latente vorm van poliomyelitis een rol zou spelen.[11] Vaccinatie voor poliomyelitis heeft wel degelijk de ziekte overwonnen, maar zeker niet het ontstaan van AIS. Recenter hebben moderne beeldvormende technieken tot theorieën geleid dat het disfunctioneren van de hersenstam of het ruggenmerg, zoals het geval bij syringomyelie of Chiari type 1 malformatie, een mogelijke oorzaak is van een subtiele onbalans van de spieren met het ontstaan van scoliose tot gevolg.[12, 13] Daarentegen functioneren veel AIS patiënten erg goed, vaak ook op atletisch gebied, tot het moment dat ze in de puberteit raken en een verkromming van de wervelkolom ontwikkelen. Na het eind van de groei hebben ze vaak geen andere anomalie dan de wervelkolomdeformiteit en zeker geen neurologische beperkingen. Het streven naar het begrijpen van de oorzaak van AIS heeft geleid tot een enorm aantal studies over het subklinische, neuromusculaire functioneren van AIS patiënten en tot het veelvuldig beschrijven van verschillende etiologische theorieën over mechanismen die mogelijk de balans van de wervelkolom beïnvloeden, bijvoorbeeld: asymmetrie van het brein, morfologie van het cerebellum, asymmetrie en verminderde propriocepsis of verminderde spierkracht paravertebraal.[14-18] Daarnaast zijn er ook nog veel niet-neurologische extrinsieke factoren bestudeerd, op zowel metabool, endocrien als genetisch gebied, die potentieel zouden kunnen leiden tot AIS.[19-23]

Welke anomalieën komen voor in AIS patiënten ten opzichte van gezonde adolescenten? Kunnen deze een extrinsieke rol spelen in de etiopathogenese van AIS?

In **hoofdstuk 2** werd een uitgebreide systematische review van de literatuur verricht met als doelstelling om een zo compleet mogelijk overzicht te geven van alle bijkomende anomalieën, die mogelijk relevant zijn voor het begrijpen van de oorzaak van AIS. In deze studie werd gevonden dat er een groot aantal anomalieën is beschreven in de literatuur die geassocieerd zijn met AIS en in verband worden gebracht met de verschillende etiologische hypotheses.[2] Hard bewijs voor een consistent patroon van gelijktijdig optreden van AIS en een van de anomalieën ontbreekt echter. Op basis van deze systematische review lijkt de relevantie van alle extrinsieke anomalieën die zijn beschreven in AIS patiënten erg gelimiteerd. Belangrijker nog, tot op heden is er geen longitudinale data beschikbaar over het bestaan van anomalieën in AIS patiënten voorafgaand aan het ontstaan van de deformiteit. Vanwege het ontbreken van deze longitudinale studies en hard bewijs uit cross-sectionele studies, lijkt het er op dat de ontwikkeling van idiopathische scoliose niet een extrinsieke, maar een intrinsieke respons is op een verstoring van de fragiele balans van de rechtopstaande menselijke wervelkolom tijdens de groei.

DE ROL VAN ACHTERWAARTS GERICHTE SCHUIFKRACHTEN IN DE ETIOPATHOGENESE

Ondanks de overeenkomsten in architectuur van de wervelkolom tussen verschillende diersoorten kan de biomechanische belasting sterk verschillen, afhankelijk van de positie in de ruimte ten opzichte van de zwaartekracht.[24-27] Eigenlijk zijn alle zoogdieren voornamelijk onderhevig aan axiale compressie alsmede ventraal gerichte schuifkrachten. De basale anatomie (brede eindplaten van de wervels, tussenwervelschijven, lokalisatie van de facetgewrichten en uitsteeksels aan de achterzijde voor aanhechting van spieren en ligamenten) maakt het mogelijk om deze krachten tegen te werken. Echter, de wijze waarop de volledig rechtopstaande menselijke wervelkolom biomechanisch wordt belast is karakteristiek voor de mens en verschilt significant van andere soorten, ook van andere bipedale zoogdieren.[5, 6, 8] De rechtopstaande menselijke wervelkolom heeft zich aangepast aan het habituele tweevoeterschap door de ontwikkeling van een secundaire lordose lumbaal, die zijn oorsprong vindt in het bekken. Dientengevolge zijn in het sagittale vlak sommige delen van de thoracale en lumbale wervelkolom van de mens naar achter gekanteld. Hierdoor zijn bij de mens, in tegenstelling tot alle andere soorten, deze naar achter gekantelde wervelniveaus onderhevig aan achterwaarts gerichte schuifkrachten.[28]

Net als achterwaarts gerichte schuifkrachten komt ook idiopathische scoliose uitsluitend bij de mens voor. Idiopathische scoliose is niet geobserveerd in andere zoogdieren.[9, 29] In 2005 introduceerden Castelein et al. een hypothese dat deze achterwaarts gerichte schuifkrachten in combinatie met pre-existente rotatie een cruciale rol spelen in de etiopathogenese van AIS.[5] In het begin van deze onderzoekslijn hebben Kouwenhoven et al. in een *ex vivo* model laten zien dat achterwaarts gerichte schuifkrachten leiden tot een verminderde rotatiestijfheid van segmenten van de wervelkolom, omdat er geen anatomische structuur is om deze krachten tegen te werken.[6] De wervelkolom van de mens is daarom rotationeel een minder stabiel construct dan elke andere wervelkolom in de natuur. Het deel van de normale wervelkolom in groeiende kinderen dat onderhevig is aan deze ongunstige belasting was slecht gedefinieerd. In 2009 toonden Janssen et al. voor asymptomatische jongvolwassenen de variatie in hoeveelheid achterwaarts gerichte belasting en het deel van de wervelkolom waarop deze krachten inwerken aan door het meten van de achteroverkanteling van wervels op gestandaardiseerde, lage dosis röntgenfoto's van de wervelkolom.[7] Er werd geconstateerd dat de wervels in verschillende spinale regio's meer naar achter gekanteld zijn in vrouwen ten opzichte van mannen en dat de naar achter gekantelde niveaus van de niet-scoliotische wervelkolom overeenkomt met de aangedane, geroteerde niveaus in AIS. Naast het concept van achterwaarts gerichte schuifkrachten die rotatie induceren, werd de hypothese geformuleerd dat, indien deze rotatie ontstaat, het reeds bestaande rotatiepatroon van de wervelkolom gevolgd zal worden.[5, 30] In meerdere studies hebben Kouwenhoven et al. en Janssen et al. gevonden dat er zowel in de normale mens als in viervoeters sprake is van een bepaald pre-existent rotatiepatroon van de wervelkolom en dat dit patroon, hoewel kleiner in omvang, overeenkomt met de richting van de rotatie in AIS.[31-33] Tot slot werd geobserveerd dat dit pre-existente rotatiepatroon van de menselijke wervelkolom gerelateerd is aan orgaanligging en lichaamspositie, niet aan handvoorkeur.[33, 34]

Om beter te begrijpen welke factoren een rol spelen in de etiopathogenese van AIS werden in het eerste deel van dit proefschrift de unieke eigenschappen van de rechtopstaande menselijke wervelkolom en het bekken, en de rol van achterwaarts gerichte schuifkrachten, rotatiestabiliteit en pre-existente rotatie onderzocht.

DE CONSEQUENTIES VAN DE MORFOLOGIE VAN HET BEKKEN EN DE WERVELKOLOM VAN DE NIET-SCOLIOTISCHE, RECHTOPSTAANDE WERVELKOLOM

Wat is de normale ontwikkeling van het sagittale profiel van bekken en wervelkolom tijdens de adolescente groeispurt?

Het is al decennialang bekend dat deformiteiten van de wervelkolom in kinderen een typische leeftijdsverdeling en verdeling tussen de geslachten kennen.[35-38] AIS ontstaat bijvoorbeeld het meest frequent in meisjes tijdens de adolescente groeispurt, de ziekte van Scheuermann komt voornamelijk in jongens van diezelfde leeftijd voor en infantiele idiopathische scoliose met name in jongens tijdens de infantiele groeispurt. Het doel van de studie gepresenteerd in **hoofdstuk 3** was om het sagittale profiel van bekken en wervelkolom en de mate van inwerking van achterwaarts gerichte schuifkrachten te typeren en te vergelijken tussen jongens en meisjes vóór, tijdens en na de adolescente groeispurt. In dit onderzoek, die werd uitgevoerd in twee centra, werden alle röntgenfoto's van kinderen zonder spinale afwijkingen geïncludeerd. De meesten waren verwezen door schoolverpleegkundigen en ondergingen een radiologische screening voor scoliose, maar bleken een niet-afwijkende wervelkolom te hebben. Daarnaast werd voor alle geïncludeerde volgroeide kinderen geverifieerd dat ze ook geen scoliose hadden ontwikkeld in de resterende groeispurt, dus na de initiële screening. In totaal werden gestandaardiseerde laterale röntgenopnamen van 156 kinderen zonder scoliose tussen de 7 en 18 jaar oud geanalyseerd. Op basis van eerder gedocumenteerde data over de volwassenwording van het skelet en het precieze tijdstip van de piek van de groeispurt, werden alle proefpersonen geclassificeerd in drie cohorten. Hierbij werd gebruik gemaakt van de sluiting van het driehoekvormige kraakbeen en de verbening van de bekkenkam (Risser stadium).[39, 40] Er waren 73 kinderen voor, 38 tijdens en 45 na de piek van de adolescente groeispurt. De resultaten toonden dat de thoracale kyfose, de kanteling van het bekken (*pelvic tilt*) en de bekkenincidentie (*pelvic incidence*) toenemen tijdens de groei en dat voor en tijdens de piek van de groeispurt relatief meer wervels naar achter gekanteld staan ten opzichte van na de piek van de groeispurt. Tevens was de wervelkolom van meisjes tijdens de piek van de groeispurt meer naar achter gekanteld in vergelijking met jongens en hadden zij een kleinere thoracale kyfose. Dit betekent dat de wervelkolom van meisjes tijdens de piek van de groeispurt onderhevig is aan relatief meer achterwaarts gerichte schuifkracht en dat deze dus relatief minder weerstand geeft tegen axiale rotatie. Dit kan verklaren waarom AIS, onder nog steeds onbekende omstandigheden tijdens de groei, vaker in meisjes voorkomt dan in jongens en dat de incidentie van de ziekte van Scheuermann hoger is in adolescente jongens.

Wat is de invloed van groei en ouder worden op de sagittale morfologie van het bekken?

Binnen de evolutie van de mens heeft het ontstaan van een lordose tussen het os ischium en os ilium mogelijk gemaakt dat wij voortbewegen in volledig rechtopstaande positie met het zwaartepunt van het lichaam recht boven het bekken en daarbij behoud van de mogelijkheid tot volledige extensie van heupen en knieën. Het is belangrijk ons te realiseren dat dit postuur essentieel verschilt van alle andere gewervelden, inclusief onze naaste verwanten, namelijk de Bonobo's. Binnen de antropologie wordt algemeen geaccepteerd dat de 'bekken-lordose' heeft geleid tot de meer horizontale positie van het sacrum in de bekkenring en de lumbale lordose en dus de typerende dubbele S-bocht van de rechtopstaande menselijke wervelkolom.[41-48] Zelfs in onze vroegste voorvader (de soort *Australopithecus afarensis*, ook bekend als "Lucy", die werd ontdekt in Ethiopië in 1974 en 3.2 miljoen jaar geleden waarschijnlijk al rechtop liep) is deze lordose terug te vinden.[48, 49] Als gevolg van de unieke configuratie van de menselijke wervelkolom in de ruimte leidt dit ook tot een unieke biomechanische belasting, met gevolgen voor verschillende spinale aandoeningen. Ook van klinische studies die de veelgebruikte parameter "bekkenincidentie" hebben onderzocht, weten we dat het bekken een belangrijke determinant is van het globale sagittale profiel van de wervelkolom.[50-52] In **hoofdstuk 4** introduceerden we een nieuwe bekkenparameter die de relatie beschrijft tussen de initiële veranderingen die we zagen in de evolutie van de mens en het profiel van de wervelkolom van de moderne mens: de ischio-iliacale hoek, oftewel de bekkenlordose. Het doel van deze studie was om voor het eerst in de literatuur de ontwikkeling van de ischio-iliacale lordose in het normale bekken te kwantificeren, van jonge kinderleeftijd tot oudere leeftijd, en om de correlatie van deze parameter met de beter bekende en veel gebruikte bekkenincidentie te evalueren. Hiervoor werden 499 gecomputeriseerde tomografische (CT) scans van het bekken van asymptomatische kinderen (n=189) en volwassenen (n=310) semiautomatisch geanalyseerd met behulp van eerder gevalideerde beeldverwerkingstechnieken (**appendix 1**). In deze observationele studie werd een grote variatie in de ischio-iliacale lordose en bekkenincidentie gevonden. Er was sprake van een significante correlatie tussen beide parameters en we observeerden dat beide toenemen tijdens de groei op kinderleeftijd en dat deze toenames stagneren na de puberteit. Ondanks het feit dat er geen positionele parameters zijn meegenomen in deze studie vanwege de liggende positie van de proefpersonen in de CT scanner, impliceert dit resultaat dat de ischio-iliacale lordose één harmonieuze continuïteit is met de lumbale lordose. Gegeven de relatie met de bekkenincidentie en de lumbale lordose vormt dit de basis van de biomechanica van de rechtopstaande wervelkolom van de mens.[50-52] In toekomstige studies kan de vraag worden beantwoord of de ischio-iliacale lordose kan worden gebruikt als een voorspellende waarde voor het ontstaan en de verergering van verschillende groei gerelateerde pathologiën van de wervelkolom zoals

AIS, spondylolisthesis, de ziekte van Scheuermann, alsmede voor degeneratieve ziektes van de wervelkolom en heupen of voor lage rugklachten.[53-56]

Wat zijn de pre-existente rotatiepatronen van de normale wervelkolom van kinderen?

Het meest voorkomende type bocht van AIS is een rechtsconvexe thoracale bocht met een compensatoire hoogthoracale en (thoraco)lumbale bocht naar links.[57] Eerder is aangetoond dat als de wervelkolom decompenseert in een scoliose, ongeacht de reden, de richting van de spinale bocht wordt bepaald door een ingebouwd rotatiepatroon van de wervelkolom.[31, 58] In tegenstelling tot adolescente scoliose is de thoracale bocht in infantiele idiopathische scoliose veel vaker geroteerd en gedevieerd naar links, terwijl in juveniele idiopathische scoliose dit patroon meer gelijk verdeeld is tussen rechts en links.[59] Het doel van de studie in **hoofdstuk 5** was om te bepalen of er een bepaald rotatiepatroon bestaat in het transversale vlak van de normale, niet-scoliotische infantiele (0-3 jaar oud), juveniele (4-9 jaar oud) en adolescente (10-16 jaar oud) wervelkolom. We hebben daarbij de rotatie van iedere individuele wervel tussen T2 en T12 gemeten op CT scans van 146 asymptomatische kinderen. Variantieanalyse onthulde significante verschillen in het rotatiepatroon van de wervelkolom tussen de drie leeftijdscohorten. Op infantiele leeftijd was de wervelkolom op alle thoracale niveaus naar links geroteerd. Op juveniele leeftijd waren de thoracale wervels georiënteerd in de middenlijn. In tegenstelling tot de infantiele en juveniele leeftijd waren op adolescente leeftijd de mid- en laagthoracale niveaus (T6-T12) significant geroteerd naar rechts, als ook eerder werd gezien in volwassenen.[31] Met dit resultaat laat onze analyse van de niet-scoliotische wervelkolom op verschillende leeftijden zien dat asymmetrie in het transversale vlak ook een eigenschap is van de normale wervelkolom in kinderen. Tevens komen de verschillende rotatiepatronen van de infantielen, juvenielen en adolescenten uit deze studie overeen met de rotatie en convexiteit van de bocht in idiopathische scoliose. Daarom wordt de hypothese, dat de convexiteit van de bocht in idiopathische scoliose wordt bepaald door een pre-existent rotatiepatroon, ondersteund.[30]

Corresponderen de pre-existente rotatiepatronen van de wervelkolom van kinderen met asymmetrische sluiting van het neurocentrale kraakbeen?

Eerder is gesuggereerd dat rotatie van de wervelkolom in idiopathische scoliose het gevolg is van asymmetrische sluiting van het neurocentrale kraakbeen (NCK).[60-62] Vanuit dit perspectief werd gedacht dat actieve unilaterale groei van het rechter NCK leidt tot axiale rotatie van de wervels naar links. Dit kan echter ook een secundair fenomeen zijn als gevolg van rotatie, in plaats van de oorzaak. Op basis van de wet van Hueter-Volkmann kan worden verwacht dat axiale rotatie van een wervel secundair zal leiden tot asymmetrische druk op het NCK, met een asymmetrisch sluitingspatroon van deze structuren tot gevolg.[63, 64] Het kan daardoor verwacht worden dat, ongeacht of het een actief of passief proces is dat leidt tot sluiting van het kraakbeen, axiale rotatie en sluiting van het NCK aan elkaar gerelateerd zijn. Deze relatie is nooit eerder onderzocht in asymptomatische kinderen. In **hoofdstuk 6** werd axiale rotatie en sluiting van het NCK bestudeerd in de thoracale en lumbale wervelkolom van in totaal 199 niet-scoliotische kinderen (inclusief de 156 kinderen van hoofdstuk 5) gebruikmakend van gedegen segmentatie software voor het meten van het absolute oppervlak van het NCK. Er werd gevonden dat de sluiting van het NCK start in de lumbale wervelkolom (L1-L3) op 4-5 jarige leeftijd, gevolgd door de laaglumbale niveaus (L4-L5) en hoogthoracale niveaus, en eindigt in de mid- en laagthoracale wervels op 8-9 jarige leeftijd. Daarnaast was in de thoracale wervelkolom op infantiele leeftijd voornamelijk het rechter NCK groter, terwijl op juveniele leeftijd het linker NCK groter was. Op adolescente leeftijd waren de meeste niveaus (90%) reeds gesloten. Met inachtneming van de resultaten van hoofdstuk 5 en 6 correspondeert het sluitingspatroon van het NCK met de rotatiepatronen van de wervelkolom van kinderen en de convexiteit van de bocht in idiopathische scoliose. De rol van actieve groei van het NCK in het ontstaan en de progressie van axiale rotatie in AIS moet gelimiteerd zijn aangezien het NCK reeds grotendeels gesloten, en dus inactief, is op adolescente leeftijd. Het pre-existente rotatiepatroon en de asymmetrische sluiting van het NCK lijkt echter de richting van de bocht te bepalen zodra een idiopathische scoliose zich ontwikkelt.

MECHANISMEN IN DE ONTWIKKELING VAN AIS

Het tweede deel van de proefschrift richtte zich op verdere exploratie van de biomechanische mechanismen in de progressie van AIS.

Wat zijn de verschillen in het sagittale profiel van wervelkolom en bekken tussen thoracale en lumbale AIS in een vroeg stadium?

Hierboven is het concept uitgelegd waarin de menselijke wervelkolom in rotatiezin een veel minder stabiel construct is dan elke andere wervelkolom in de natuur: Rotatiestijfheid van spinale segmenten die naar achter gekanteld zijn is verminderd door achterwaarts gerichte schuifkrachten en de naar achter gekantelde wervels in de menselijke wervelkolom corresponderen met de geroteerde segmenten in AIS.[5, 8] Dit concept verschilt aanzienlijk van bijvoorbeeld het concept van Dickson et al. waarin idiopathische scoliose start als een thoracale lordose, terwijl in ons concept lordose juist een gevolg is van rotatie, niet de oorzaak.[28, 37, 65] Op basis van ons concept kan worden geconcludeerd dat het deel van de wervelkolom waarin een rotatoire deformiteit kan ontstaan, is gebaseerd op verschillen in het sagittale profiel vóór het ontstaan van de deformiteit. De hypothese dat thoracale AIS ontwikkelt in een ander sagittaal profiel dan (thoraco)lumbale AIS werd onderzocht in een internationale twee-centrum studie. Deze wordt gepresenteerd in **hoofdstuk 7**. Om het causale verband tussen sagittaal profiel van de wervelkolom en het ontstaan van AIS te onderzoeken, zouden we idealiter willen beschikken over longitudinale data van het sagittale profiel op juveniele leeftijd, voorafgaand aan het ontstaan van de deformiteit, omdat het sagittale profiel van de wervelkolom wordt aangetast door de deformiteit zelf. Echter, omdat het zowel praktisch als ethisch vrijwel onmogelijk is om een dergelijke studie uit te voeren, gebruikmakend van röntgenstraling in asymptomatische kinderen, hebben we gekozen voor uitvoering van een studie met de één na beste opzet om de hypothese te testen. Uit een multicenter database van bijna 1400 AIS patiënten werden alle kinderen geselecteerd met laterale röntgenopnamen van de wervelkolom die een nog erg kleine (Cobb hoek kleiner dan 20 graden) thoracale (Lenke 1 en 2, n=128) of thoraco(lumbale) scoliose (Lenke 5, n=64) hadden. Tevens hebben we röntgenopnamen van niet-scoliotische personen verzameld als controlegroep. Systematische analyse van het sagittale profiel en de exacte kanteling van iedere individuele wervel – dezelfde methode als gebruikt in hoofdstuk 3 en een eerdere studie[66] – onthulde dat zelfs in een zeer vroeg stadium, de achterwaartse kanteling en thoracale kyfose van thoracale AIS verschilt van (thoraco)lumbale AIS en ook van de controlegroep. In meer detail, in thoracale scoliose waren de meeste thoracale wervels meer naar achter gekanteld ten opzichte van (thoraco)lumbale scoliose en vice versa. Onze opzet was niet uniek. Andere onderzoekers hebben ook mogelijke verschillen in het sagittale profiel van bekken en wervelkolom onderzocht tussen verschillende types AIS, maar de meesten hebben naar de globale parameters thoracale kyfose en lumbale lordose gekeken, zonder rekening te houden met de biomechanische lading van de wervelkolom.[67-69] Analoog aan onze eerdere studies demonstreren de resultaten van deze studie dat de naar achter gekantelde segmenten van de wervelkolom corresponderen met de geroteerde segmenten in verschillende types van AIS. Dit verschil in sagittaal profiel was al aanwezig in een zeer vroeg stadium tijdens de ontwikkeling van de rotatie en de bocht in AIS. Het kan daarom worden aangenomen dat dit een rol speelt in de pathogenese van verschillende type bochten. Dit is in overeenstemming met het eerder besproken etiologische concept.

Wat is de ware 3-D morfologie van AIS?

Moderne chirurgische technieken richten zich op het zo goed mogelijk herstellen van de wervelkolom tot de normale anatomie. Begrip van de ware 3-D morfologie van de wervelkolom in AIS is zowel vanuit theoretisch oogpunt als voor de dagelijkse praktijk belangrijk, aangezien beiden begrip van de ware aard van de aandoening vereisen.

Achttiende- en negentiende-eeuwse anatomen hebben de 3-D morfologie van scoliotische verkrommingen destijds in veel detail beschreven in *post-mortem* studies.[1, 70, 71] Het belang van het sagittale profiel werd zeer gewaardeerd in die tijd, als duidelijk wordt van een verklaring van Meyer in 1866: "*Aus den angegebenen Grunden findet man: mit jeder Skoliose der Brustgegend verbunden einen entsprechenden Grad der (relativen oder absoluten) Lordose*" (in het Nederlands: Gebaseerd op de bovenstaande gronden is het zo dat men bij iedere thoracale scoliose een overeenkomstige mate van (relatieve of absolute) lordose ziet).[71] Echter, vanaf de introductie van röntgengrafie werd scoliose langzaamaan beschouwd als een deformiteit in het coronale vlak, tot een aantal auteurs nogmaals het belang van het sagittale vlak gingen benadrukken.[65, 72-75] Uiteindelijk heeft dit geleid tot de aanname dat idiopathische scoliose een probleem kan zijn van een gegeneraliseerde overvloed aan anterieure groei van de wervelkolom, of een discrepantie tussen de groei van het ruggenmerg ten opzichte van de groei van de wervels.[76-80] Ondanks dat het 3-D aspect van AIS al meer dan een eeuw is onderzocht, met name de laatste jaren, is de ware 3-D morfologie, en met name het sagittale profiel van de verschillende regio's van de scoliotische wervelkolom, nog nooit eerder in detail beschreven.

Sinds 2011 hebben alle AIS casus die zijn geopereerd in de Chinese University of Hong Kong preoperatief hogeresolutie CT van de wervelkolom ondergaan voor navigatie doeleinden. Deze unieke dataset, alsmede een dataset van CT scans van normale kinderen (gemaakt voor niet-gerelateerde indicaties als trauma, longziekten, etcetera), werd gebruikt voor het onderzoek gepresenteerd in **hoofdstuk 8**. De scans zijn geanalyseerd met behulp van speciale software waarmee vectoren van de eindplaten konden worden gereconstrueerd en de 3-D deformiteit in het coronale, transversale en ware sagittale vlak van verschillende regio's van de wervelkolom van AIS patiënten gedetailleerd kon worden geanalyseerd. Deze kwantitatieve beschrijving van de 3-D morfologie van AIS is interessant, want deze toont dat (1) de 3-D ontwikkeling van de bochten in AIS een uniform patroon volgen met daarbij directe koppeling van de vervorming in alle drie de vlakken, en dat (2) alle bochten in AIS, zowel structureel als niet-structureel, primair en secundair, thoracaal en (thoraco)lumbaal, gekenmerkt worden door een relatief grotere anterieure lengte van Cobb eindwervel tot Cobb eindwervel in het ware sagittale vlak. De overgangszones tussen de bochten waren daarentegen min of meer recht.

Waar is de 3-D deformiteit in AIS gelokaliseerd, in de discus of wervellichamen?

In tweedimensionale (2-D) studies naar de morfologie van AIS die gebruik hebben gemaakt van röntgenfoto's zijn tegenstrijdige bevindingen gerapporteerd over de individuele bijdrage van de wervellichamen ten opzichte van de tussenwervelschijven aan de coronale deformiteit in AIS.[81-90] Daarnaast is gesuggereerd dat mogelijk actieve groeifenomenen en ziektes van botmetabolisme een etiologische rol spelen in AIS. In

hoofdstuk 9 wordt de belangrijke vraag beantwoord in welke anatomische structuur en in welk vlak de deformiteit ontstaat in AIS. In deze studie werden de individuele bijdragen van zowel de disci als wervellichamen aan de 3-D deformiteit van de wervelkolom geanalyseerd. Dezelfde serie hoge-resolutie CT scans en software werden gebruik als in hoofdstuk 8. Voor deze studie werden voor iedere patiënt segmentale parameters bepaald voor iedere discus (totaal, n=924) en wervel (totaal, n=1078) tussen de niveaus T4 en L5. In tegenstelling tot eerdere 2-D studies werd gevonden dat in AIS de intervertebrale disci minimaal drie keer meer gedeformeerd waren in het coronale, ware transversale en ware sagittale vlak dan de wervellichamen.[86, 88] De voor-achterwaartse en coronale wigvorming was meer uitgesproken rond de apex van de bochten, terwijl mechanische torsie in alle spinale regio's werd gezien. De gezamenlijke conclusie van hoofdstuk 8 en 9 is dat de overmaat aan anterieure lengte in AIS niet een globaal probleem is dat wordt gezien in de gehele wervelkolom, maar een regionale eigenschap is. De deformiteit in AIS is daarom een passief proces in plaats van actieve skeletale groei, omdat de deformiteit meer in de discus aanwezig is dan in het bot.

IMPLICATIES VOOR CLINICI DIE AIS PATIËNTEN BEHANDELEN

Het primaire doel van scoliosechirurgie is altijd het voorkomen van verergering geweest. Tevens wordt getracht een goed gebalanceerde wervelkolom in het coronale en sagittale vlak te verkrijgen, het aantal gefuseerde wervels te minimaliseren en eventuele complicaties te voorkomen. Er is echter bewijs dat zo goed mogelijk herstel tot normale anatomie ten gunste komt van de niet-gefuseerde overgebleven delen van de wervelkolom.[91-93] Zelfs met moderne chirurgische technieken blijft het lastig om de normale vorm van de wervelkolom te verkrijgen en om problemen als thoracale hypokyfose en overgangsdecompensatie te voorkomen. Voor corrigerende scoliosechirurgie is het essentieel om volledig begrip te hebben van de deformiteit van de wervelkolom in alle drie de dimensies en de obstakels tijdens de reductie. Voor de beoordeling van de *in vivo* 3-D morfologie wordt hoge-resolutie CT als gouden standaard gezien. Deze techniek heeft echter het nadeel dat de beelden alleen in liggende positie kunnen worden verkregen. Uit praktisch oogpunt demonstreren we in **hoofdstuk 8** hoe de ware 3-D morfologie kan worden voorspeld op basis van metingen op conventionele 2-D staande röntgenopnamen.

Welk effect hebben posterieure klievingen over meerdere segmenten op de beweeglijkheid van de wervelkolom?

In hoofdstuk 8 werd gedemonstreerd dat de voorzijde van de wervelkolom in AIS van bovenste Cobb eindwervel tot onderste Cobb eindwervel relatief te lang is ten opzichte van de normale anatomie. Er zijn twee mogelijke oplossingen voor deze overmaat aan anterieure lengte: posterieure verlenging of anterieure inkorting. De posterieure benadering is de meest gebruikte techniek in de behandeling van scoliose, maar gebaseerd op onze analyse kan worden verondersteld dat anterieure technieken niet dienen te verdwijnen, en mogelijk een opleving dienen te krijgen indien met maximale posterieure verlenging niet het gewenste resultaat wordt behaald. Bij de posterieure benadering is het nu niet duidelijk hoeveel posterieure ligamenten gekliefd moeten worden om voldoende verlenging van de posterieure zijde van de wervelkolom te verkrijgen en deze te herstellen naar een normaal sagittaal profiel. In de biomechanische studie, gepresenteerd in **hoofdstuk 10**, hebben we de effectiviteit van verschillende stapsgewijze posterieure klievingen van ligamenten, die veelvuldig worden gebruikt in de chirurgische praktijk voor het verlengen van de posterieure zijde van de thoracale wervelkolom, getest. In een eerder gevalideerd *ex vivo* model werd de bewegingsvrijheid van niet-scoliotische, thoracale preparaten onderzocht na opeenvolgende klievingen, inclusief een volledige Ponte osteotomie.[95] Het verwijderen van de posterieure ligamenten gaf meer flexibiliteit in zowel het sagittale, coronale als transversale vlak en leidt dus tot betere correctiemogelijkheden in alle drie de vlakken. Er wordt gedemonstreerd hoeveel flexie er kan worden verkregen door iedere stap. Deze data kan daarom dienen als chirurgische richtlijn. Superieure facetectomie, als wordt vervaardigd in een complete Ponte osteotomie, had geen klinisch relevante toegevoegde waarde (0.1 graden extra flexie per segment) voor het verkrijgen van extra beweeglijkheid in het sagittale vlak na eerdere achtereenvolgende losmaking van de supra- en interspinale ligamenten en het ligamentum flavum en verwijdering van de inferieure facetten. Als de resultaten van hoofdstuk 8 en 10 worden gecombineerd, lijkt toevoeging van posterieure verlengingsmethoden aan de posterieure benadering een goede optie om ongeveer 8% extra posterieure lengte te verkrijgen van Cobb eindwervel tot Cobb windwervel om de normale thoracale kyfose te reconstrueren.[96] Tevens zouden anterieure inkortingsmethoden door bijvoorbeeld discectomiën of wigresecties valide opties zijn als maximale correctie in alle drie de vlakken gewenst is.[95, 97]

Kunnen we de gereviseerde Scoliosis Research Society 22-item vragenlijst vertalen en aanpassen voor gebruik in Nederland?

Vanwege toenemende interesse, ook van Nederlandse spinaal chirurgen, voor het meten van gezondheid gerelateerde kwaliteit van leven in patiënten met AIS wordt in **hoofdstuk 11** de gereviseerde Scoliosis Research Society 22-item vragenlijst vertaald naar het Nederlands, aangepast aan Nederland en gevalideerd.[98] Na dit proces werd geconcludeerd dat de Nederlandse SRS-22r de eigenschappen heeft die nodig zijn voor het meten van gezondheid gerelateerde kwaliteit van leven van AIS patiënten in Nederland. Dusver heeft deze patiënt gerapporteerde vragenlijst al aan acceptatie gewonnen in verschillende delen van Nederland en wordt deze gebruikt in longitudinale onderzoeken om het effect van moderne conservatieve en invasieve behandelingen van AIS patiënten te onderzoeken.

EINDCONCLUSIE EN TOEKOMSTPERSPECTIEF

Voorafgaand aan dit promotieonderzoek was het al bekend dat onder bepaalde omstandigheden (als er een disbalans is tussen de werkende kracht en het compenserende mechanisme van het lichaam) een overmaat aan axiale compressie van de adolescente wervelkolom een deformiteit kan veroorzaken die bekend is als de ziekte van Schueurmann.[35] Op vergelijkbare wijze kan een overmaat aan voorwaarts gerichte schuifkrachten leiden tot spondylolisthesis.[53, 54] In dit proefschrift worden de gevolgen voor de balans van de wervelkolom van een derde kracht, die uniek is voor de mens en inwerkt op bepaalde segmenten van de rechtopstaande wervelkolom, bestudeerd: achterwaarts gerichte schuifkrachten.

In het kort, met verschillende cross-sectionele onderzoeken wordt in dit proefschrift bewijs geleverd voor het concept dat AIS het gevolg is van verminderde rotatiestijfheid van de wervelkolom door een overmaat aan achterwaarts gerichte schuifkrachten. Onze studies laten ook zien dat als de wervelkolom decompenseert in een idiopathische scoliose, het rotatiepatroon wordt gevolgd dat pre-existent is in de normale wervelkolom. Dit leidt uiteindelijk tot de ontwikkeling van geroteerde lordosen rond de apices van de bochten en deze verkromming van de wervelkolom heeft een significant effect op gezondheid gerelateerde kwaliteit van leven. We kunnen concluderen dat AIS een intrinsieke biomechanische basis heeft: Een disbalans tussen de biomechanische belasting van de rechtopstaande wervelkolom (dat wil zeggen achterwaarts gerichte schuifkrachten) aan de ene kant en de compensatoire mechanismen van het lichaam aan de andere kant.[5]

Voor verdere opheldering van de etiopathogenese van AIS en de rol van achterwaarts gerichte schuifkrachten is er noodzaak voor een grootschalig onderzoek naar de veranderingen in het sagittale profiel van de wervelkolom, waarbij kinderen die het risico lopen om een idiopathische scoliose te ontwikkelen worden gevolgd van jongs af aan (dus nog vóór de groeispurt) tot volwassenheid. Moderne lage-dosis 3-D beeldvormende technieken of digitale houdingsmetingen zouden kunnen helpen om de ethische bezwaren te weerleggen als het gaat om een longitudinale studie met röntgenstraling in asymptomatische kinderen.[94, 99] Bovendien zou een populatie die een groter risico loopt AIS te ontwikkelen, zoals jonge familieleden van AIS patiënten of kinderen met het

22q11 deletie syndroom, kunnen helpen bij het maximaliseren van de doeltreffendheid van een dergelijke longitudinale studie.[36, 100] Daarmee zou kunnen worden geverifieerd met welk sagittaal profiel de wervelkolom van een kind aanleg heeft voor het ontstaan van AIS, de ziekte van Scheuermann of een normale ontwikkeling, en of hiermee eventuele progressie kan worden voorspeld.

Tot slot blijft de volgende vraag bestaan: "Wat is het onderliggende mechanisme en wat is de de onderliggende structuur die de rotatiestabiliteit van de wervelkolom beïnvloedt en een kind blootstelt aan de ontwikkeling van een rotatoire deformiteit, terwijl andere kinderen asymptomatisch blijven?" In een van onze studies werd gezien dat in AIS de geometrie van de discus in vergelijking met de wervellichamen het meest is aangedaan. Tevens speelt deze structuur een essentiële rol in de rotatiestabiliteit van de pediatrische en volwassen wervelkolom. Vanuit ons perspectief zou een onderzoek naar de factoren die de rotatiestabiliteit van de tussenwervelschijf beïnvloeden een eerste stap zijn om de bovenstaande vraag te beantwoorden. Moderne, niet-ioniserende beeldvormende technieken, zoals bijvoorbeeld T1ρ of T2-mapping magnetische resonantie, zouden hierbij kunnen helpen.[101]

Zolang het onderzoek naar de etiologie en pathogenese van AIS doorgaat, kan worden verwacht dat de onderliggende biologische en mechanische mechanismen worden ontdekt en dat mogelijke risicofactoren voor het ontstaan en verergeren van AIS kunnen worden geïdentificeerd in een vroeg stadium, als minder invasieve behandelmethoden nog een optie zijn. Dit is nodig om adequate causale behandelmethoden te ontwikkelen, omdat vooralsnog de behandeling van AIS met name gericht is op de behandeling van late gevolgen van de vervorming van de wervelkolom.

List of Abbreviations and Definitions

2-D	Two-dimensional
3-D	Three-dimensional
95%CI	95% confidence interval
#DV	Number of declive vertebrae
(T)L	Thoracolumbar curve
ΔA-P	Anterior-posterior length difference
ΔR-L	Right-left length difference
μ_{AIS}	Mean outcome of AIS cases
$\mu_{controls}$	Mean outcome of healthy adolescents
σ	Standard deviation
AIS	Adolescent idiopathic scoliosis (10-16 years old)
ANOVA	Analysis of variance
Apex	The most laterally deviated vertebra or disc in a scoliotic curve in the coronal plane
AR	Axial rotation
Axial rotation	Rotation in the transverse plane around the anterior-posterior axis of the body
CHQ-CF87	Child Health Questionnaire – Child Form 87
Cobb	Angle between lines drawn on endplates of the end vertebrae
$Cobb_{MT}$	Cobb angle of the main thoracic curve
$Cobb_{(T)L}$	Cobb angle of the (thoraco)lumbar curve
COM	Center of mass
CT	Computed tomography
CT & CV	Bilateral costotranversectomy and costovertebralectomy
DL	Declive length
End vertebrae	The cranial and caudal vertebrae that bound a scoliotic curve in the coronal plane
FL	Resection of the flaval ligament
HA	Hip-axis
ICC	Intraclass correlation coefficient
Idiopathic	A disease that is not linked to any physical impairment or previous medical history. (in Greek: ίδιος=one's own and πάθος=suffering)
IF	Bilateral inferior facetectomy
IIA	Ischio-iliac angle
IIS	Infantile idiopathic scoliosis (0-3 years old)
IVD	Intervertebral disc
JIS	Juvenile idiopathic scoliosis (4-9 years old)
Kyphosis	Forward curvature of a part of the spine in the sagittal plane
LB	Lateral bending
LL	Lumbar lordosis
Lordosis	Backward curvature of a part of the spine in the sagittal plane
MAD	Mean absolute difference
MANOVA	Multivariate analysis of variance
MIP	Maximum intensity projection

MRI	Magnetic resonance imaging
MT	Main thoracic curve
n.s.	Not significant
n/a	Not applicable
NCJ	Neurocentral junction
Non-structural curve	A scoliotic curve on a supine maximal lateral side bending radiograph of which the Cobb angle corrects to a value lower than 25 degrees.
P	Statistical significance
PA	Postero-anterior radiography
PI	Pelvic incidence
PROM	Patient Related Outcome Measure
PT	Pelvic tilt
r	Pearson's correlation coefficient
ROM	Range of motion
Scoliosis	A curvature of the spine more than ten degrees in the coronal plane
sd or SD	Standard deviation
se	Standard error
SF	Bilateral superior facetectomy
SF-36	Short Form 36-item patient questionnaire
SL & IL	Resection of the supraspinous and interspinous ligament
SRS	Scoliosis Research Society
SRS-22	Scoliosis Research Society 22-item patient questionnaire
SRS-22r	Revised Scoliosis Research Society 22-item patient questionnaire
SS	Sacral slope
Structural curve	A scoliotic curve on a supine maximal lateral side bending radiograph of which the Cobb angle corrects to a value 25 degrees or more.
T9SO	T9 sagittal offset
TK	Thoracic kyphosis
Torsion	Deformation due to relative axial rotation
VAS	Visual analog scale for pain
Vertebral inclination	Inclination of the lower endplate of a vertebra in the sagittal plane.
VOI	Volumes of interest

Acknowledgement, List of Publications, Curriculum Vitae

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LIST OF PUBLICATIONS

This thesis

1. Chapter 2: **Schlösser TP**, van der Heijden GJMG, Versteeg AL, Castelein, RM.
   How 'idiopathic' is adolescent idiopathic scoliosis? A Systematic Review on Associated Abnormalities.
   PLoS One, 2014 May 12;9(5):e97461. doi: 10.1371/journal.pone.0097461.

2. Chapter 3: **Schlösser TP**, Shah SA, Rogers KJ, Vincken KL, Castelein RM.
   Natural Sagittal Spino-Pelvic Alignment in Boys and Girls Before, At and After the Adolescent Growth Spurt.
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3. Chapter 4: **Schlösser TP**, Janssen MM, Vrtovec T, Pernuš F, Öner FC, Viergever MA, Vincken KL, Castelein RM.
   Evolution of the Ischio-Iliac Lordosis during Natural Growth and its Relation with the Pelvic Incidence.
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4. Chapter 5: Janssen MM, Kouwenhoven JW, **Schlösser TP**, Viergever MA, Bartels LW, Castelein RM, Vincken KL.
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5. Chapter 6: **Schlösser TP**, Janssen MM, Attrach H, Vincken KL, Castelein RM.
   Quantitative analysis of the closure pattern of the neurocentral junction as related to preexistent rotation in the normal immature spine.
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7. Chapter 8: **Schlösser TP**, van Stralen M, Chu WC, Lam TP, Ng BK, Vincken KL, Cheng JC, Castelein RM.
   The True Three-Dimensional Deformity of the Spine in Adolescent Idiopathic Scoliosis

8. Chapter 9: **Schlösser TP**, van Stralen M, Brink RC, Chu WC, Lam TP, Ng BK, Vincken KL, Castelein RM, Cheng JC.
   Three-Dimensional Characterization of Torsion and Asymmetry of the Intervertebral Discs versus Vertebral Bodies in Adolescent Idiopathic Scoliosis.
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9. Chapter 10: Holewijn R, **Schlösser TP**, van der Veen AJ, Bisschop A, Smit T, Castelein RM, de Kleuver M.
   How Much does a Ponte Osteotomy Contribute to Spinal Flexibility in Scoliosis Surgery?

10. Chapter 11: **Schlösser TP**, Stadhouder A, Schimmel JJ, Lehr AM, van der Heijden GJ, Castelein RM.
    Reliability and Validity of the Adapted Dutch Version of the revised Scoliosis Research Society 22-item questionnaire.
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Other papers

11. Homminga J, Lehr AM, Meijer GJ, Janssen MM, **Schlösser TP**, Verkerke GJ, Castelein RM; Posteriorly Directed Shear Loads and Disc Degeneration Affect the Torsional Stiffness of Spinal Motion Segments: A Biomechanical Modelling Study. *Spine (Phila Pa 1976). 2013 Jun 21.*

12. Yue JJ, Telles C, **Schlösser TP**, Hermenau S, Ramachandran R, Long III WD, Do Presence and Location of Annular Tear Influence Clinical Outcome following Lumbar Total Disc Arthroplasty? A prospective one year follow up study.
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13. Colo D, **Schlösser TP**, Oostenbroek H, Castelein RM, Complete Remodeling After Conservative Treatment of A Severly Angulated Odontoid Fracture in a Patient with Osteogenesis Imperfecta: A case report.

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1. **Schlösser TP**, van Stralen M, Chu WC, Lam TP, Ng BK, Vincken KL, Cheng JC, Castelein RM; Quantitative Analysis of the Three-Dimensional Morphology of Adolescent Idiopathic Scoliosis (AIS) with Implications for Surgical Strategy. 49th Scoliosis Research Society Annual Meeting 2014, Anchorage, AL, USA
2. **Schlösser TP**, van Stralen M, Brink RC, Chu WC, Lam TP, Ng BK, Vincken KL, Castelein RM, Cheng JC. Three-Dimensional Characterization of Torsion and Asymmetry of the Intervertebral Discs versus Vertebral Bodies in Adolescent Idiopathic Scoliosis. 49th Scoliosis Research Society Annual Meeting 2014, Anchorage, AL, USA
3. **Schlösser TP**, van Stralen M, Chu WC, Lam TP, Ng BK, Vincken KL, Cheng JC, Castelein RM; The True 3-D Morphology of Adolescent Idiopathic Scoliosis. Nordic Spinal Deformity Society Annual Meeting, 2014, Oslo, Norway.
4. **Schlösser TP**, van Stralen M, Brink RC, Chu WC, Lam TP, Ng BK, Vincken KL, Castelein RM, Cheng JC. A Computed Tomography-Based Study on Asymmetry and Intrinsic Torsion of the Intervertebral Discs versus Vertebral Bodies in Adolescent Idiopathic Scoliosis. Nordic Spinal Deformity Society Annual Meeting, 2014, Oslo, Norway.
5. **Schlösser TP**, van der Heijden GJMG, Versteeg AL, Castelein, RM. How 'Idiopathic' is Adolescent Idiopathic Scoliosis? A Systematic Review on Associated Abnormalities. Nordic Spinal Deformity Society Annual Meeting, 2014, Oslo, Norway.
6. **Schlösser TP**, Shah SA, Rogers KJ, Vincken KL, Castelein RM. Sagittal Spino-Pelvic Alignment in Boys and Girls Before, At and After Adolescent Peak Height Velocity. . International Research Society for Spinal Deformities, 2014, Sapporo, Japan.
7. **Schlösser TP**, van Stralen M, Brink RC, Chu WC, Lam TP, Ng BK, Vincken KL, Castelein RM, Cheng JC. Three-Dimensional Characterization of Torsion and Asymmetry of the Intervertebral Discs versus Vertebral Bodies in Adolescent Idiopathic Scoliosis. International Research Society for Spinal Deformities, 2014, Sapporo, Japan.
8. **Schlösser TP**, van Stralen M, Chu WC, Lam TP, Ng BK, Vincken KL, Cheng JC, Castelein RM; Quantitative Analysis of the 3-D Morphology of Adolescent Idiopathic Scoliosis with Implications for Surgical Strategy. International Research Society for Spinal Deformities, 2014, Sapporo, Japan.
9. **Schlösser TP**, van Stralen M, Brink RC, Chu WC, Lam TP, Ng BK, Vincken KL, Castelein RM, Cheng JC; A Computed Tomography-Based Study On Asymmetry And Intrinsic Torsion Of The Intervertebral Discs Versus Vertebral Bodies In Adolescent Idiopathic Scoliosis. European Pediatric Orthopedic Society Annual Meeting 2014, Bruges, Belgium.
10. **Schlösser TP**, Shah SA, Rogers KJ, Vincken KL, Castelein RM. Natural Sagittal Spino-Pelvic Alignment In Boys And Girls Before, At And After The Adolescent Peak Height Velocity. European Pediatric Orthopedic Society Annual Meeting 2014, Bruges, Belgium.

11. **Schlösser TP**, Janssen MM, Vrtovec T, Pernuš F, Öner FC, Viergever MA, Vincken KL, Castelein RM. The Development Of The Ischio-Iliac Lordosis During Growth As An Essential Adaptation Towards Human Bipedalism And A Determinant Of Sagittal Balance. European Pediatric Orthopedic Society Annual Meeting 2014, Bruges, Belgium.
12. **Schlösser TP**, Van Stralen M, Chu WC, Vincken KL, Castelein RM, Cheng JC. Quantitative Estimation of the Three-Dimensional Morphology of Adolescent Idiopathic Scoliosis. Dutch Orthopaedic Society Annual Meeting 2014, Rotterdam, The Netherlands.
13. **Schlösser TP**, Shah SA, Rogers K, Vincken KL, Castelein RM; Natural Sagittal Spino-Pelvic Alignment in Boys and Girls, Before, At and After the Peak of the Adolescent Growth Spurt. Dutch Orthopaedic Society Annual Meeting 2014, Rotterdam, The Netherlands.
14. **Schlösser TP**, Van Stralen M, Chu WC, Vincken KL, Castelein RM, Cheng JC. Quantitative Estimation of the Three-Dimensional Morphology of Adolescent Idiopathic Scoliosis. ImagO Autumn Conference, 2013, Utrecht, The Netherlands.
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16. **Schlösser TP**, Shah SA, Rogers K, Vincken KL, Castelein RM; Natural Sagittal Spino-Pelvic Alignment in Boys and Girls Before, At and After the Adolescent Growth Spurt, Nordic Spinal Deformity Society Annual Meeting, 2013, Denmark.
17. **Schlösser TP**, Janssen MM, Vrtovec T, Pernuš F, Öner FC, Viergever MA, Vincken KL, Castelein RM. Development of Ischio-Iliac Lordosis as an Essential Adaptation Towards Human Bipedalism and a Determinant of Sagittal Balance. Nordic Spinal Deformity Society Annual Meeting, 2013, Denmark.
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19. **Schlösser TP**, Janssen MM, Attrach H, Kuijf H. Vincken KL, Castelein RM, Analysis of the Neurocentral Junction in the Normal Infantile, Juvenile and Adolescent Spine. EuroSpine, Spineweek, 2012, Amsterdam, The Netherlands.
20. **Schlösser TP**, Janssen MM, Attrach H, Vincken KL, Castelein RM; Analysis of the Neurocentral Junction in the Normal Infantile, Juvenile and Adolescent Spine. International Research Society Spinal Deformities meeting, 2012, Poznan, Poland.
21. **Schlösser TP**, Janssen MM, Attrach H, Vincken KL, Castelein RM, Closure patterns of the Neurocentral Junction in Relation to Preexistent Rotation in the Normal Infantile, Juvenile and Adolescent Spine. European Paediatric Orthopaedic Society Annual meeting, 2012, Helsinki, Finland.

22. **Schlösser TP**, Janssen MM, Castelein RM, Preexistent rotation of the normal spine at different ages and its consequences for the scoliotic mechanism. Annual Science Meeting, Division of Surgical Specialities, University Medical Center Utrecht, 2012, Utrecht, Netherlands.
23. **Schlösser TP**, Janssen MM, Attrach H, Vincken KL, Castelein RM, Analysis of the Neurocentral Junction in the Normal Infantile, Juvenile and Adolescent Spine. International Conference for early onset scoliosis, 2012, Orlando, FL, USA.
24. **Schlösser TP**, Janssen MM, Attrach H, Vincken KL, Castelein RM, Sluiting van het neurocentrale kraakbeen in de onvolgroeide wervelkolom, Dutch Orthopaedic Society Annual Meeting, 2011, The Hague, The Netherlands.
25. Janssen M, Kouwenhoven JW, **Schlösser TP**, Castelein RM, Analysis of Preexistent Vertebral Rotation in the Normal Infantile, Juvenile and Adolescent Spine, Scoliosis Research Society Annual Meeting, 2011, Kyoto, Japan.
26. Yue JJ, MD, Garcia R, MD, **Schlösser TP**, A Prospective Clinical Comparison of 3 Biomechanical Types of Lumbar Disc Replacements: A Semi-Constrained Device, A Controlled Translation Device, and An Unconstrained Device Minimum 2 year follow-up, 10th Annual SAS Global Symposium on Motion Preservation Technology, 2010, New Orleans, LA, USA.
27. Telles C, Hermenau S, **Schlösser TP**, Ramachandran R, Yue JJ, Do Presence and Location of Annular Tear Influence Clinical Outcome following Lumbar Total Disc Arthroplasty? A prospective one year follow up study. NASS 25th Annual Meeting, 2010, Orlando, FL, USA.

Abstracts (poster presentations)

28. **Schlösser TP**, Shah SA, Rogers K, Vincken KL, Castelein RM; Natural Sagittal Spino-Pelvic Alignment in Boys and Girls Before, At and After Adolescent Peak Height Velocity; 49th Scoliosis Research Society Annual Meeting 2014, Anchorage, AL, USA. E-poster presentation
29. **Schlösser TP**, van der Heijden GJMG, Versteeg AL, Castelein, RM. How 'Idiopathic' is Adolescent Idiopathic Scoliosis? A Systematic Review on Associated Abnormalities. International Research Society for Spinal Deformities, 2014, Sapporo, Japan.
30. **Schlösser TP**, Janssen MM, Vrtovec T, Pernuš F, Öner FC, Viergever MA, Vincken KL, Castelein RM. The development of the ischio-iliac lordosis during growth as an essential adaptation towards human bipedalism and a determinant of sagittal balance. International Research Society for Spinal Deformities, 2014, Sappora, Japan.
31. **Schlösser TP**, van Stralen M, Chu WC, Lam TP, Ng BK, Vincken KL, Cheng JC, Castelein RM. A High Resolution CT Study on the Intra-operative Three-Dimensional Morphology of Adolescent Idiopathic Scoliosis. European Pediatric Orthopedic Society Annual Meeting 2014, Bruges, Belgium. E-poster presentation

32. **Schlösser TP**, Shah SA, Reichard S, Rogers K, Vincken KL, Castelein RM; Differences in Sagittal Spino- Pelvic Alignment between different types of Adolescent Idiopathic Scoliosis, and Controls. EuroSpine, 2013, Liverpool, UK. E-poster presentation.
33. **Schlösser TP**, Janssen MM, Attrach H, Vincken KL, Castelein RM, Analysis of the Neurocentral Junction in the Normal Infantile, Juvenile and Adolescent Spine. Orthopaedic Research Society Annual Meeting, 2012, San Francisco, CA, USA. Poster presentation
34. Yue JJ, MD, Garcia R, MD, **Schlösser TP**, A Prospective Clinical Comparison of 3 Biomechanical Types of Lumbar Disc Replacements: A Semi-Constrained Device, A Controlled Translation Device, and An Unconstrained Device Minimum 2 year follow-up, Spine Arthroplasty Society Annual Meeting, 2009, London, UK. Poster presentation.

CURRICULUM VITAE

The author of this thesis was born in Heerlen, The Netherlands on May 25, 1987 and grew up with two older brothers. In 2005, he graduated *cum laude* from high school (VWO, Bernardinuscollege, Heerlen) and started medical school at the Utrecht University in the Netherlands. In 2009 he started his research career at the department of Orthopaedic Surgery, University Medical Center Utrecht, Utrecht, the Netherlands, under supervision of prof. dr. René M. Castelein and dr. Michiel M.A. Janssen. At 23 years of age, he performed a research fellowship on the feasibility of disc prostheses at the department of Orthopedic Surgery and Rehabilitation, Yale New Haven Hospital/Yale School of Medicine, New Haven, CT, USA (supervisor Dr. James J. Yue). Thereafter, he was soon invited by prof. dr. René M. Castelein to continue in the scoliosis research group. In December 2011 the author completed his medical degree and received a grant from the Alexandre Suerman MD-PhD Talent Programme (a personal grant to facilitate his PhD-project). In January 2012 he continued his doctoral program as a full-time medical doctor and PhD-candidate on the etio-pathogenesis of idiopathic scoliosis at the University Medical Center Utrecht. The research was performed in close collaboration with image processing experts and he was supervised by prof. dr. René M. Castelein, prof. dr. Max A. Viergever and dr. Koen L. Vincken. International collaborative projects were initiated and in 2012 and 2013 the author performed an international research fellowship at the Department of Orthopaedics, Alfred I DuPont Hospital for Children, Wilmington, Delaware, USA (supervisor: Dr Suken A. Shah) and took part in the International Asia Studies Programme at the department of Orthopaedics and Traumatology, Chinese University of Hong Kong, Shatin, Hong Kong (supervisor: professor Jack C. Cheng). The present work has resulted in numerous presentations at prestigious international conferences, peer-reviewed publications and this thesis. In December 2013 he started his training in orthopaedic surgery at the department of General Surgery at the St. Antonius Ziekenhuis in Nieuwegein (head: Dr. P.M.N.Y.H. Go), after which he will continue in orthopaedic surgery at the Onze Lieve Vrouwe Gasthuis in Amsterdam, Diakonessenhuis Utrecht, University Medical Center Utrecht and St. Antonius Ziekenhuis in Nieuwegein.