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IDIOPATHIC SCOLIOSIS - ASPECTS ON SURGICAL AND NON - SURGICAL TREATMENT

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Cover illustration: This is what scoliosis looks like through the eyes of an 8 year old child; the author´s daughter.

Idiopathic scoliosis-aspects on surgical and non-surgical treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To all our patients.

ABSTRACT

The term scoliosis has been used to describe conditions that lead to deformation of the spine. It derives from the ancient Greek '*σκολίωσις*' and the root word '*σκολιός*' which means 'bent or crooked'. In its most common form, scoliosis is of unknown - idiopathic - cause and origin. It affects roughly 3% of children and adolescents during growth and in mild cases no treatment is required. In moderate cases, bracing has been proposed, with the aim to halt progression of idiopathic scoliosis. It is most common with full-time bracing using rigid, custom made thoracolumbosacral orthoses. It is worn for 16-20 hours per day until skeletal maturity and has been shown to prevent scoliosis progression to a surgical threshold in about 70% of the cases. However, compliance to the treatment has been one of the major drawbacks seen with the full-time brace. Therefore, night-time braces, worn only during the night, have started to gain popularity over the years. Nevertheless, evidence on the effectiveness of night-time bracing has only been based on retrospective studies. More recently, specific scoliosis exercise regimes consisting of self-mediated correction maneuvers in 3 dimensions have also emerged. So far, there has been only one high quality study showing effectiveness of this modality, in patients with mild idiopathic scoliosis.

A trial was performed consisting of 135 patients randomized to self-mediated physical activity in combination with either night-time brace, or scoliosis-specific exercise, or self-mediated physical activity alone. Night-time brace was shown to be more effective than self-mediated physical activity in preventing scoliosis progression. On the other hand, scoliosis-specific exercise did not show any clinical benefit when compared to the self-mediated physical activity. Additionally, comparison between the nigh-time brace group and a group of patients who declined participation in the trial and received a full-time brace showed similar effectiveness on the prevention of curve progression.

In case the deformity progresses to more severe curves, surgery may be suggested. Over the last decades, a posterior exposure to the spine with a high number of implants and predominantly pedicle screw based fixation techniques has been favored over traditional techniques with low number of implants for the correction of scoliosis. These techniques have been suggested to increase correction and fusion rates and eliminate the risks associated with exposure of the chest wall and/or abdomen in anterior approaches to the spine. Disadvantages of the posterior approach to the spine include extended muscle dissection, need for a higher number of vertebrae to be fused and risk for neurological injuries to the spinal cord. To date, whether posterior based fusion may result in better clinical and radiographic outcomes compared to anterior fusion is still unclear. Moreover, whether higher number of implants per vertebra (implant density) results in better clinical and radiographic outcomes is still debatable.

In a nationwide registry-based cohort, we identified patients who underwent anterior (n=27) and posterior (n=32) fusion surgery for a thoracolumbar/lumbar type of scoliosis. We found that despite a longer operative time in the anterior group and higher blood loss and longer fusion constructs in the posterior group, both procedures resulted in significant correction of the

scoliosis with similar patient-reported outcome and satisfaction; suggesting that the type of approach is not related to health-reported quality of life.

By using the same nationwide database, we also identified 328 surgically treated idiopathic scoliosis patients who were then divided into tertiles based on the number of implants used per operated vertebra. We found no differences in the correction rate of the curve and health-reported quality of life in the different tertiles, suggesting that a high number of implants is not necessarily beneficial in the surgical treatment of idiopathic scoliosis.

Studies have shown that, what is perceived as successful radiographic outcome, may not necessarily correlate with patient´s own perception of successful outcome after surgery for idiopathic scoliosis. Patients may still experience persistent back pain and worse quality of life, despite an excellent radiographic outcome.

By using the same nationwide database, we identified 280 patients treated with posterior fusion surgery for idiopathic scoliosis and divided them into a high (n=67) and a low (=213) postoperative pain group, based on their self-reported postoperative back pain scores. We found that patients in the high pain group also reported higher back pain and worse quality of life before surgery, compared to the low postoperative pain group. High preoperative back pain and low preoperative mental health were identified as predictors of persistent pain after surgery.

SUMMARY IN SWEDISH (SAMMANFATTNING PÅ SVENSKA)

Ordet skolios betyder ryggradskrökning. Det härstammar från grekiskans ‘σκολίωσις’ och ordet ” σκολιός” betyder böjd eller krökt. Orsaken till den vanligaste formen av skolios är okänd och kallas idiopatisk. Idiopatisk skolios drabbar ungefär 3 % av barn och ungdomar. Milda skolioser behöver ingen behandling. Större skolioser kan behandlas med korsett för att minska risken för en ökning av skoliosen. En av de vanligaste typerna av korsett som används är en så kallad dygnetruntkorsett som används större delen av dygnet tills man växt färdigt. Denna behandling kan minska risken för ökning av skoliosen i 70% av fallen. En av de största nackdelarna med dygnetruntkorsett har varit den bristande följsamheten. Därför har nattkorsetten ökat i popularitet de senaste åren, då den bara behöver användas en begränsad tid av dygnet. Det vetenskapliga stödet för att det finns en effekt av behandling med nattkorsett är baserat på retrospektiva studier. Skoliosspecifik träning är en annan behandling för skolios som ökat i popularitet. Hittills finns det bara en studie med hög kvalitet som visar effekt av denna behandling och då hos patienter med mild idiopatisk skolios.

I en randomiserande studie med 45 personer i varje grupp testade vi effekten av behandling med nattkorsett eller skoliosspecifik träning jämfört med en kontrollgrupp. Oavsett grupp fick alla instruktioner att utföra minst 60 minuters fysisk aktivitet per dag. Nattkorsetten minskade risken för en ökning av skoliosen jämfört med kontrollgruppen. Skoliosspecifik träning minskade inte risken för en ökning av skoliosen jämfört med kontrollgruppen. Vi jämförde också gruppen som fick behandling med nattkorsett med en grupp som valde att avstå från att delta i studien och i stället fick behandling med en dygnetruntkorsett. Vi såg ingen skillnad i risk för ökning av skoliosen mellan dessa två grupper.

I de fall då skoliosen ökade till mer allvarliga krökar, så föreslogs kirurgi. När det gäller kirurgi så har typen av behandling skiftat över tid. De senaste två decennierna har en så kallad bakre operation varit vanligast. En så kallad främre operation där operation sker från sidan genom brösthålan är just nu mindre vanlig. För- och nackdelar med dessa tekniker har ofta diskuterats.

Med hjälp av ett nationellt kvalitetsregister, det svenska ryggregistret, så identifierade vi 27 patienter som genomgått främre och 32 patienter som genomgått bakre kirurgi för skolios belägen i övergången mellan bröst och ländrygg. De som genomgick främre kirurgi hade längre operationstider, medan de som opererades med bakre kirurgi hade större blodförluster och blev opererade över fler kotor. Oavsett typ av operation så sågs god korrektion av skoliosen med liknande patientrapporterat utfall och nöjdhet. Även om vår studie var relativt liten så talar den och andra studier för att det inte spelar någon roll vilken teknik man använder.

Med hjälp av ryggregistret så identifierade vi 328 patienter opererade för idiopatisk skolios som sedan delades in i tre grupper baserat på hur många ryggimplantat som använts per opererad kota. Vi såg ingen skillnad på grad av uträtning eller patientrapporterade utfall i de tre grupperna, vilket antyder att ett större antal implantat per opererad kota inte nödvändigtvis är fördelaktigt vid kirurgisk behandling av idiopatisk skolios.

Det är sedan tidigare känt att graden av korrektion av en skolioskrök under operation inte alltid är direkt relaterad till patientens uppfattning om resultatet. Genom att använda det nationella ryggregistret identifierade vi 280 patienter som var behandlade med bakre kirurgi för idiopatisk skolios och delade in dem efter grad självrapporterad smärta efter operationen, de som hade hög grad av smärta (67 stycken) och de som hade låg grad av smärta (213 stycken). Vi såg att patienter i gruppen med hög grad av smärta efter operationen också rapporterade en hög grad av smärta och en sämre livskvalitet innan operationen jämfört med patienterna i gruppen med låg smärta. Hög grad av smärta och nedsatt mental hälsa innan operationen förutspådde hög grad av smärta efter operationen.

LIST OF SCIENTIFIC PAPERS

I. **Implant density is not related to patient-reported outcome in the surgical treatment of patients with idiopathic scoliosis.**
Anastasios Charalampidis, Anders Möller, Marie-Louise Wretling, Torkel Brismar, Paul Gerdhem

The Bone & Joint journal. 2018 Aug;100-B(8):1080-1086.

II. **Predictors of persistent postoperative pain after surgery for idiopathic scoliosis.**
Anastasios Charalampidis, Lina Rundberg, Hans Möller, Paul Gerdhem

Journal of Children´s Orthopaedics. 2021 Oct 1;15(5):458-463.

III. **Anterior versus posterior fusion surgery in idiopathic scoliosis: a comparison of health-related quality of life and radiographic outcomes in Lenke 5C curves - results from the Swedish spine registry.**
Anastasios Charalampidis, Hans Möller, Paul Gerdhem

Journal of Children´s Orthopaedics. 2021 Oct 1;15(5):464-471.

IV. **Effectiveness of night-time brace and scoliosis-specific exercise for the treatment of adolescent idiopathic scoliosis: results of a multicenter randomized controlled trial.**
Anastasios Charalampidis, Elias Diarbakerli, Marlene Dufvenberg, Kourosh Jalalpour, Acke Ohlin, Anna Aspberg Ahl, Hans Möller, Allan Abbott, Paul Gerdhem, on behalf of the CONTRAIS study group

Manuscript

V. **Effectiveness of night-time bracing and full-time bracing in the treatment of adolescent idiopathic scoliosis.**
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CONTENTS

LIST OF ABBREVIATIONS

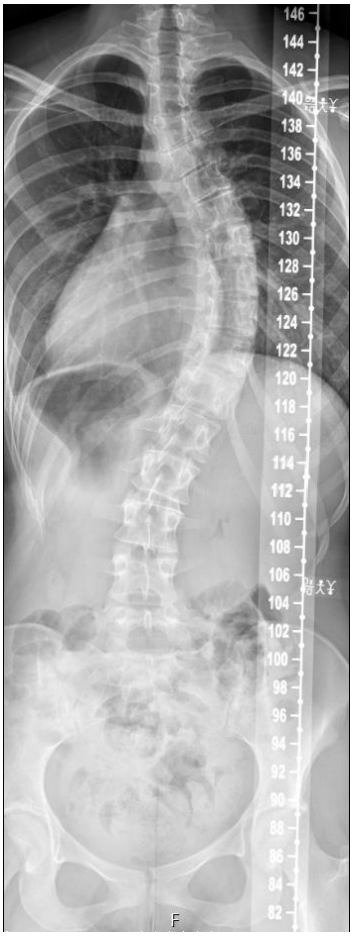
CNS	Central nervous system
MRI	Magnetic resonance imaging
CSF	Cerebrospinal fluid
FBT	Forward bending test
ATR	Angle of trunk rotation
CSVL	Central sacral vertical line
PA	Posteroanterior
AIS	Adolescent idiopathic scoliosis
RCT	Randomized controlled trial
SRS-22r	Scoliosis research society 22r instrument
EQ-5D-3L	EuroQol-5 dimension quality of life, three level
EQ-5D-3L-Y	EuroQol-5, youth version
EQ VAS	EuroQol visual analogue scale
VAS	Visual analogue scale
OR	Odds ratio
CI	Confidence interval
PSSE	Physiotherapeutic scoliosis-specific exercise
SEAS	Scientific exercise approach to scoliosis
Swespine	Swedish spine registry
CONTRAIS	CONservative TReatment for Adolescent Idiopathic Scoliosis
SOSORT	Society on scoliosis orthopaedic and rehabilitation treatment

1 LITERATURE REVIEW

1.1 BACKGROUND

Idiopathic scoliosis is defined as a three-dimensional structural deformity of the spinal column and is usually associated with trunk asymmetry [1, 2] (*Figure 1*). It is the most common type of scoliosis affecting otherwise healthy children and has no clear identifiable cause [3]. Epidemiological studies estimated the prevalence of idiopathic scoliosis to be around 3% [3]. Definite diagnosis is made by measuring the curves of the deformity, using the Cobb method [4]; on a standing posteroanterior radiograph, the Cobb angle is formed by drawing a line parallel to the superior and to the inferior endplates of the vertebrae included in the scoliotic curve. Scoliosis is then diagnosed if the Cobb angle is ≥10°. While the majority of the patients with idiopathic scoliosis will not require treatment [5], around 10% of patients with progressive scoliosis will require further treatment in order to prevent long term health problems such as respiratory dysfunction and back pain [6].

Figure 1. Standing radiograph of a patient with a thoracic curve type of AIS.



1.2 AETIOPATHOGENESIS

The aetiopathogenesis of idiopathic scoliosis is poorly understood [7]. Several hypotheses have been proposed; these can be categorized - based on the type of changes they describe - into: Genetics, central nervous system (CNS) disorders, disorders in bone metabolism and biomechanics [8-42].

1.2.1 Genetics

There are several studies in the literature that show a strong genetic component in patients with idiopathic scoliosis. Wynne-Davis et al. reported an increased risk of developing idiopathic scoliosis in family members of individuals with scoliosis [8]. Moreover, in a twin study based on the Swedish Twin Registry, Grauers et al. found the relative importance of genetic basis on heritability for scoliosis to be 38% [9].

Although there is no debate about the genetic basis of idiopathic scoliosis, little is known about the genetic variants expressed in patients with idiopathic scoliosis [10]. Several studies reported associations between idiopathic scoliosis and specific genes [11-18]; a large-scale genome-wide association study (GWAS) in Japan, found common variants near LBX1 gene to be associated with adolescent idiopathic scoliosis [19]. This association was reported in other Asian studies as well [20-22]. Recently, Kou et al. [23] found that alterations in GPR126 gene were associated with idiopathic scoliosis in humans. This genetic variability in idiopathic scoliosis, raised the notion of a more complex multigenic inheritance in which genetic and environmental factors could contribute independently to the initiation and progression of the scoliotic curve [43-46].

1.2.2 Central nervous system

Improvements in MRI technology have renewed interest in central nervous system abnormalities seen in patients with idiopathic scoliosis. Recent studies showed an association between neuromorphological abnormalities - at both the spinal cord and the brain – and idiopathic scoliosis [24-30]. MRI investigations on individuals with severe idiopathic scoliosis showed that there may be a disproportional growth between the skeletal and the neural elements [31]; the spinal cord may be shorter in relation to the spinal column. In addition, a light descent of the cerebellar tonsils (cerebellar tonsila ectopia) can be observed [24, 26]. This concept, known as uncoupled or asynchronous neuro-osseous growth, may contribute to the development of scoliosis [24, 31]. More recently, a new theory on the aetiopathogenesis of idiopathic scoliosis has arisen; Grimes et al. [32], using mutant zebrafish scoliotic models,

demonstrated that cerebrospinal fluid (CSF) flow defects may be the underlying cause of idiopathic scoliosis.

1.2.3 Bone metabolism

It is well known that idiopathic scoliosis onset and progression is related to skeletal immaturity and to pubertal growth spurt. During this period of accelerated growth, abnormal bone growth and abnormal bone metabolism may occur, as reported in numerous studies [33, 34]. These abnormalities may be expressed as generalized low mineral density (osteopenia), abnormal bone mineral status and abnormal morphometry and have been found to be associated with idiopathic scoliosis [35-37, 47], although fracture risk seems to be unaffected [42].

1.2.4 Biomechanics

The role of biomechanics in the development of idiopathic scoliosis is not well established. Theories have emerged over the last years relating the unique - among vertebrates – human spino-pelvic complexity in the upright position to idiopathic scoliosis. Bipedalism (the ability to stand and walk on two legs) has been the driving force behind significant skeletal changes in the human species [38] such as the lordotic lumbar spine and the center of gravity above the hips [39, 40]. Consequently, the biomechanical loading of the human spine differs significantly from the one of other vertebrates, with specific regions of the human spine subject to dorsal shear loading forces [40, 41]. In this context, recent studies showed that dorsal shear loading of the spine, as seen in humans, may lead to rotational instability and, thus, to the development of idiopathic scoliosis [41].

1.3 DIAGNOSIS

The majority of individuals with idiopathic scoliosis manifest the condition as they enter in the pubertal growth spurt [48]. On this basis, various screening programs have been developed around the world with the purpose to detect individuals with scoliosis at an early stage in early adolescence [49, 50]. The benefits of these programs were reported in studies that showed a significant decline in surgical rates for idiopathic scoliosis [51].

Clinically, patients with idiopathic scoliosis may present with shoulder height asymmetry, elevated scapula, waist asymmetry and coronal trunk shift. However, in small deformities patients may have a near normal appearance. Several screening tests such as the forward bending test (FBT), the measurement of angle of trunk rotation (ATR) measured with the scoliometer and in some countries photostereometric methods such as the Moire' topography

have been adopted for the clinical assessment of idiopathic scoliosis [52, 53]. These tests were found to be effective in detecting patients with scoliosis at an early stage [52].

Nevertheless, definite diagnosis of idiopathic scoliosis is made after radiographic assessment [54]. This includes upright posteroanterior radiograph of the entire spine. After ruling out other pathologies, such as congenital or other structural anomalies, the diagnosis is determined when a lateral curvature of the spine with an angle of at least 10 degrees is measured according to the Cobb method [54]. Lateral upright radiograph of the entire spine may add important information regarding the sagittal profile. The most common type of curve in patients with idiopathic scoliosis is the right convex thoracic curve with a secondary/compensatory left convex thoracolumbar/lumbar curve [55]. Atypical curves, such as left sided thoracic curves, C-shaped curves and short and angulated curves are not as common and warrant further investigation with MRI in order to exclude intraspinal abnormalities [5, 56]. Besides atypical curves, MRI of the spine is suggested when there is a suspicion of neurologic abnormalities on physical examination [57].

1.4 CLASSIFICATION

Idiopathic scoliosis is further classified into infantile (0-3 years), juvenile (3-10 years), and adolescent (>10 years) based on age of onset [58]. While juvenile and adolescent scoliosis have similar natural course, treatment methods and long-term outcomes [42, 59, 60], infantile scoliosis follows a different natural history and has a different prognosis; due to a greater impact on pulmonary function associated with pulmonary development during the first years of life [61, 62].

Idiopathic scoliosis may also be categorized according to radiographic parameters. For this purpose, several classification systems were introduced [63, 64]. In 1983, King et al. [63] proposed a classification system with five thoracic curve types; moreover, treatment recommendations on levels to be included in the arthrodesis were proposed. Although this system gained popularity, several limitations were identified; at that point in time, there was a growing body of evidence pointing out the importance of sagittal profile in idiopathic scoliosis [65]; the King classification system did not take into account the sagittal plane. Moreover, some studies found only poor to fair reliability, validity, and reproducibility in this classification system [66, 67]. In an effort to address these limitations, Lenke et al. introduced a new idiopathic scoliosis classification system in 2001 [64]. In the Lenke classification system, six curve types (1-6) were identified, based on the location of the curve. Curves were described as structural or non-structural; structural curves were defined as those with at least 25° Cobb angle

on supine bending radiographs or more than 20° of kyphosis on a lateral standing radiograph. This system emphasized the importance of sagittal profile and, therefore, a thoracic sagittal parameter (modifier) - measured as thoracic kyphosis from T5 to T12 - was taken into consideration; less than 10° of kyphosis was indicated with "-", > 40° of kyphosis with "+", and "N" (normal) was kyphosis in the range of 10° to 40°. Finally, three types of lumbar modifiers (A, B, C) were indicated in order to describe the relationship between the central sacral vertical line (CSVL) and the apex of the lumbar curve. Currently, the Lenke classification system is being widely used in the surgical decision making in patients with idiopathic scoliosis and studies have shown improved reliability compared with the King system [68, 69].

1.5 TREATMENT

The aim of treatment in patients with idiopathic scoliosis is to prevent progression of the condition and consequently prevent sequelae, such as back pain, pulmonary dysfunction, psychosocial concerns and early mortality [61, 70, 71]. Certain factors were found to be associated with curve progression; these include skeletal immaturity, curve magnitude, curve location, age of menarche and amount of remaining growth calculated by various skeletal maturity scoring systems [34, 72-74]. In this context, the most common modalities for the treatment of idiopathic scoliosis are physiotherapeutic scoliosis-specific exercise (PSSE), brace treatment and surgical treatment.

1.5.1 Physiotherapeutic scoliosis-specific exercise (PSSE)

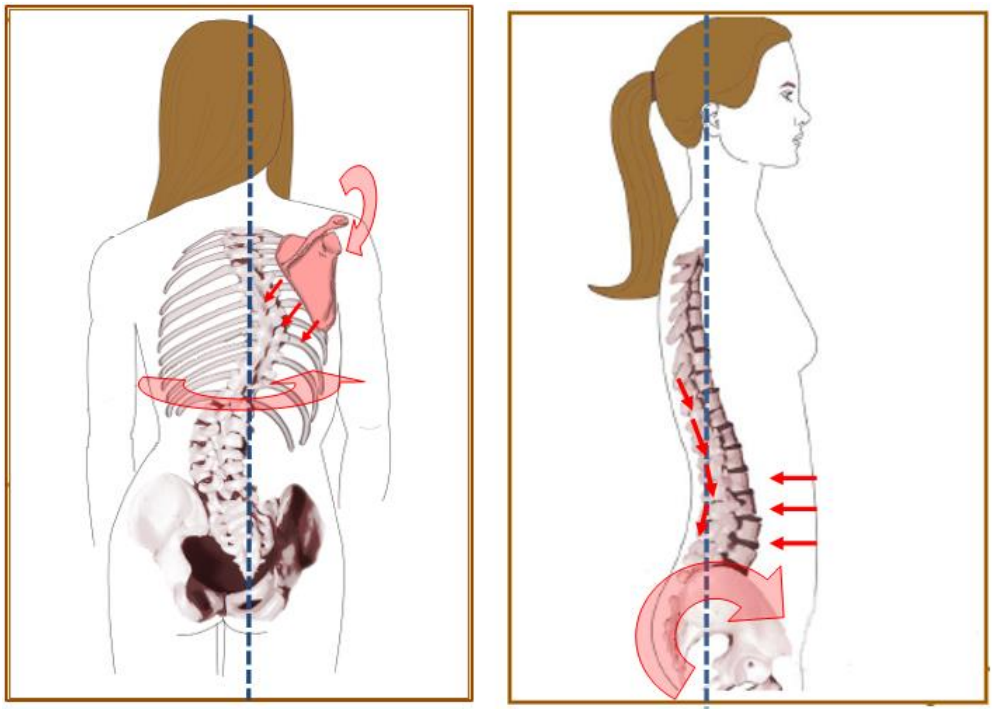
PSSE is an individualized specific physical therapy program given to a patient with idiopathic scoliosis [75] (*Figure 2*). There are several kinds of physical therapy methods used in idiopathic scoliosis [76]. Two methods gained popularity over the last years: The Schroth method [77] and the scientific exercise approach to scoliosis (SEAS) method [76].

The Schroth method was introduced in 1920 and since then has gained popularity as a physical therapy modality in idiopathic scoliosis [77]. It consists of a combination of movements and breathing techniques based on patient's unique scoliotic pattern [78]. A recently published meta-analysis reported a positive effect of this modality to prevent curve progression in patients with mild to moderate curves (10° - 30° Cobb angle)[79].

The SEAS method is based on active self-correction and stabilization exercises and can be performed by the patient on an outpatient basis or at home [80]. Recent studies showed the effectiveness of this intervention to reduce the risk of progression in mild curves [81].

Overall, there is a growing body of evidence suggesting effectiveness of PSSE in the non-surgical treatment of patients with idiopathic scoliosis [82]. In the light of these new studies, guidelines from the International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment (SOSORT) suggest physical therapy as the first step to treat mild idiopathic scoliosis and to prevent the risk of curve progression [83]. SOSORT suggests that PSSE should consist of active self-correction in 3 dimensional planes (3D), stabilizing the corrected posture, integration in activities of daily living (ADL) and patient education.

Figure 2. Example of active self-correction in 3D for active correction of AIS.



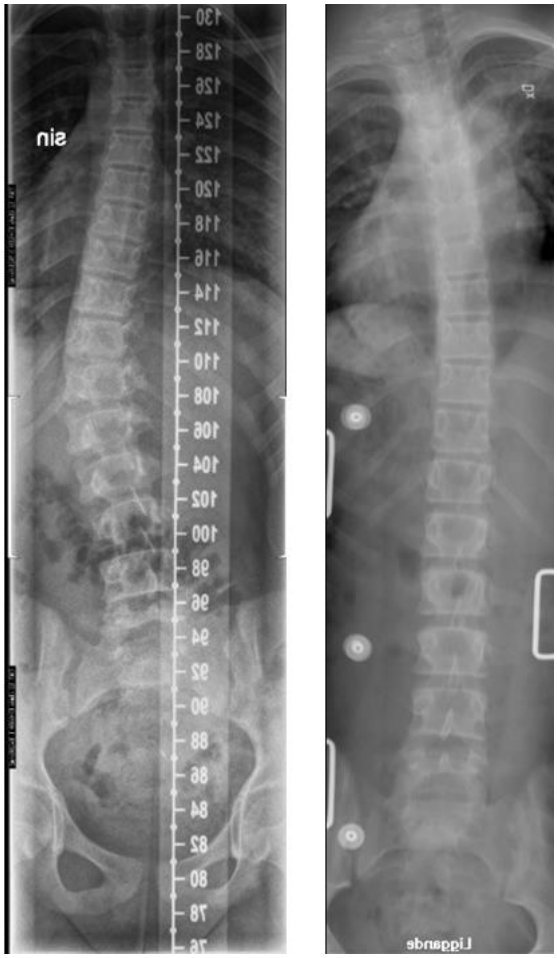
1.5.2 Brace treatment

Patients with remaining growth and skeletal immaturity are at the highest risk for curve progression. For those with scoliotic curves of less than 25 degrees of Cobb angle, observation is usually recommended while brace treatment is suggested in cases of curves with a Cobb angle of 25 degrees or more [84] (*Figure 3*). The purpose of brace treatment is to prevent progression of the curve and consequently the risk of surgery, until the patient reaches skeletal maturity; then, the risk of curve progression declines significantly. Although there are many types of braces, all serve the same cause; to halt progression of scoliosis during the growing phase [85]. Until some years ago, there was no clear evidence as to whether bracing reduces the risk of curve progression. In year 2013, the results of a clinical trial in North America highlighted the benefit of bracing in preventing curve progression and need for surgery by more

than 70% compared to observation only [86]. The same study showed a dose-response relationship between brace wearing and benefit [86]. Hence, current recommendation suggests brace wearing 16-20 hours per day.

Besides full-time braces, night-time braces have been proposed for the treatment of idiopathic scoliosis. A night-time brace is worn for a limited amount of time and could counteract compliance issues and negative impact on quality of life observed in patients treated with full-time braces [6, 87]. Results from observational studies suggest that approximately eight hours of night-time bracing with an over-corrective brace was as effective as bracing during 23 hours per day [88, 89]. Although retrospective studies suggest that night-time brace could be an attractive alternative to full-time brace [90], there is a need for high quality clinical trials evaluating its effectiveness in patients with idiopathic scoliosis.

Figure 3. Standing radiograph of a patient with a thoracolumbar/lumbar curve type without brace (*left*) and a supine radiograph in a night-time brace (*right*).

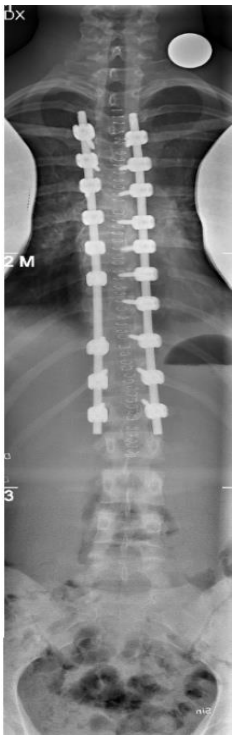


1.5.3 Surgical treatment

Surgery in idiopathic scoliosis is reserved for adolescents with curves greater than 45-50 degrees measured in a standing coronal radiograph using the Cobb method [54, 91]. The purpose of surgical treatment in these individuals with remaining growth is to arrest further progression, achieve correction of the deformity and improve cosmesis by balancing the spine in order to prevent long-term complications such as pulmonary dysfunction and back pain [5, 91].

Surgical technique usually includes spinal arthrodesis of all the structural curves; multiple anchors (pedicle screws and/or hooks) are attached to the spine and are then used over contoured rods to correct the deformity [92, 93] (*Figure 4*). Surgical access to the spine can be made by either anterior or posterior approach. Anterior surgery provides satisfactory correction of the deformity in all planes with fewer fusion levels [94-97]. Limitations of anterior approach include higher pseudarthrosis rates, a more visible surgical scar, kyphosing tendency and possible pulmonary dysfunction [98-100]. Posterior surgery started to evolve with the introduction of the Harrington rod in the 1960's [101]. After the introduction of pedicle screw fixation systems, posterior surgery has gained popularity and has prevailed in modern deformity surgery. Studies have reported better rates of correction, better sagittal alignment and similar complication rates compared to anterior approach [100, 102, 103]. Limitations of posterior approach include extensive soft tissue dissection and longer fusion constructs compared to anterior surgery [104].

Figure 4. Postoperative standing radiograph of a patient who underwent posterior correction and fusion surgery for AIS.



1.6 QUALITY OF LIFE

Over the last decades, there has been a tremendous shift in terms of the way we evaluate treatment outcome in idiopathic scoliosis. Self-reported outcome measures evaluating patients own perception on treatment outcome and quality of life gained popularity [105-107]. In this context, numerous generic and specific outcome measure tools have been developed [108-111].

Early studies on the natural history of the condition have shown that untreated idiopathic scoliosis may be associated with back pain, pulmonary dysfunction and psychosocial issues [6, 61, 70, 112-115]. However, the impact of these conditions on the overall quality of life is still debatable since the results from various studies are conflicting.

Weinstein et al. [70] reported that patients with untreated idiopathic scoliosis had higher frequency of back pain compared to individuals without the condition. On the contrary, Ascani et al. [112] found no difference in the frequency of back pain compared to the general population. Nevertheless, in both studies, back pain was not found to be a cause of disability in everyday life.

Several studies reported slightly impaired physical function and mental health after brace or surgical treatment for idiopathic scoliosis [113, 114]. Recently, Diarbakerli et al. [116] found similar health-related quality of life in adulthood between individuals with idiopathic scoliosis treated either with brace or observation only before the age of 20. Moreover, untreated individuals reported marginally higher quality of life when compared to surgically treated individuals. Contrary to the results of this study, Helenius et al. [115], in retrospective single center study with 5 year follow-up, found that surgically treated idiopathic scoliosis patients reported less back pain and improved quality of life compared to untreated individuals with idiopathic scoliosis. Interestingly, apart from lower function, surgically treated patients in this study reported similar health-related quality of life compared to a healthy control group.

Concerns have been raised regarding the impact of curve magnitude on pulmonary function [70]. Earlier studies highlighted the association between curve magnitude, pulmonary compromise and early death in idiopathic scoliosis patients with severe curves [117-120]. This may be the case in younger patients with early onset idiopathic scoliosis (0-5 years of age) [61]. However, in patients with juvenile and adolescent idiopathic scoliosis, large thoracic curves with a Cobb angle > 50°, were associated with reduced vital capacity but rarely with severe pulmonary compromise and early mortality [61, 112, 121]. Moreover, in another

retrospective study Pehrsson et al. [122] found improved pulmonary function in patients treated either with brace or surgery. This improvement was maintained at follow-up 25 years after brace treatment or surgery.

Psychosocial concerns have also been reported in patients with idiopathic scoliosis. In a study by Danielsson et al. [6] a considerable 25% of adults who were treated as youngsters with either Milwaukee or Boston brace, reported that the brace treatment period had a major negative impact on their lives. In other studies, untreated older patients with idiopathic scoliosis were less satisfied with their body appearance and one third also reported reduced physical ability and self-consciousness compared to individuals without scoliosis [70, 71].

1.7 CONCLUSION

All in all, there is a growing body of evidence suggesting that idiopathic scoliosis has an impact on quality of life. In the absence of long-term natural history data, decision making for the treatment of idiopathic scoliosis is based on the magnitude of the scoliotic curve and the risk of progression. However, what really causes idiopathic scoliosis in still poorly understood. Future studies should focus on the aetiopathogenesis of scoliosis; this would enhance our understanding of this condition and would enable the development of better treatment strategies.

2 RESEARCH AIMS

The primary aim of this thesis was to explore and expand current knowledge on the effectiveness of different treatment modalities in the conservative treatment of patients with idiopathic scoliosis. Secondary aims were to investigate clinical outcomes and quality of life in patients treated surgically for idiopathic scoliosis. Specifically, we aimed to answer the following research questions:

- Are there significant differences on the effectiveness of night-time brace or scoliosis-specific exercise in addition to self-mediated physical activity to prevent scoliosis progression when compared to self-mediated physical activity alone?

- Which type of brace, night-time or full-time, is better to prevent scoliosis progression?

- Which type of approach, anterior or posterior, is better in surgery for idiopathic scoliosis?

- Is a high number of implants per operated vertebra associated with better outcome compared to low number of implants per operated vertebra ?

- What are the factors associated with persistent postoperative pain after surgery for idiopathic scoliosis ?

3 MATERIALS AND METHODS

3.1 STUDY POPULATION

3.1.1 The Swedish spine registry

Papers I, II and III are based on data collected from the Swedish spine registry (Swespine) [123]. Swespine is a national quality registry founded in 1993. The aim of the registry is to increase the quality of surgical care in Sweden by prospectively collecting data on patients treated surgically for spinal pathologies. Preoperative, 1, 2, 5 and 10 year patient self-reported questionnaires are mailed to the patients by the registry administrator. These questionnaires are answered by the patient without any assistance from health care providers. Additionally, surgeon-reported data at the time of surgery are collected in the registry. Swespine contains information on surgeries for spinal deformity since 2006. Currently, Swespine has a coverage of 98% and a completeness of 85% [123]. Its diagnostic accuracy is estimated to be 97% [55, 124].

3.1.2 CONTRAIS trial

Papers IV and V are based on prospectively collected data from the CONservative TReatment for Adolescent Idiopathic Scoliosis (CONTRAIS) trial. Detailed information on the trial can be found in the corresponding papers (IV and V) and the published protocol [125]. The CONTRAIS trial was designed as a multicenter randomized trial and conducted in an effort to address the knowledge gap on the effectiveness of night-time brace treatment and scoliosis-specific exercise treatment in patients with adolescent idiopathic scoliosis. Six screening sites across Sweden invited patients who met the inclusion criteria to participate in the trial. Inclusion criteria were as followed: nine to 17 years of age, at least one year of remaining growth in body height, premenarche or maximum 1 year after menarche for girls, scoliotic curve with angle between 25 to 40 degrees measured according to the Cobb method and apex of the curve at the 7^{th} thoracic vertebra or caudal. One hundred thirty-five patients were included in the study and randomized in a 1:1:1 ratio into one of the three arms of the study: Self-mediated physical activity in combination with 1) night-time brace, 2) scoliosis-specific exercise, or 3) self-mediated physical activity alone. Written informed consent was obtained by all patients and/or parents before the randomization. The randomization sequence was prepared a priori by an independent statistician. Patients in the trial were followed clinically and radiographically at 6 month intervals up to skeletal maturity (treatment success). In cases of curve progression of > 6 degrees of Cobb angle (treatment failure) the patients were offered either transition to a full-time brace or - if the curve had progressed into the surgical magnitude - surgical treatment. Additional follow-ups were scheduled 2, 5 and 10 years after the primary endpoint (treatment success or treatment failure). Patients who declined participation in the randomized trial were offered the standard of care which was a full-time brace. This cohort was

also followed-up clinically and radiographically - according to local routines at each intervention site - until skeletal maturity unless surgery occurred before maturity.

3.2 OUTCOME MEASURES

3.2.1 Radiographic measurements

Radiographic assessment of standing posteroanterior and lateral radiographs of the spine was conducted in Papers I, III, IV and V. General parameters recorded are shown in the following table (*Table 1*).

Table 1. General radiographic measurements.

Paper I	**Paper III**	**Paper IV and V**
• Cobb angle of the major and secondary curves. • Direction of the convexity. • Apical Vertebral Rotation of the major curve. • Number of implants (Screws, hooks wires).	• Cobb angle of the major curve. • Direction of the convexity. • Thoracic Kyphosis T2-T12. • Lumbar Lordosis L1-S1. • Coronal angulation of the disk below the lowest instrumented vertebra. • Number of implants.	• Cobb angle of the major and secondary curves. • Direction of the convexity. • Apex of the scoliotic curve(s). • Thoracic Kyphosis T2-T12 and T5-T12. • Lumbar Lordosis T12-S1. • C7 plumbline versus CSVL.

Specific radiographic measurements and calculations included: 1) The flexibility of the major curve on bending films using the formula: [(preoperative Cobb angle - bending Cobb angle)/(preoperative Cobb angle)] × 100 [126], 2) the implant density, as total number of implants divided by number of levels fused [55], 3) the correction of the major curve using the formula: [(preoperative Cobb angle - postoperative Cobb angle) / (preoperative Cobb angle)] x 100% [126], (*Papers I and III*) and 4) in-brace correction according to the formula: [(Cobb angle on standing PA radiograph – Cobb angle on in-brace radiograph)/ Cobb angle on standing PA radiograph)] x 100 [127, 128], (*Paper V*).

Radiographic measurements were conducted through radiographic images in Digital Imaging and Communications in Medicine (DICOM) image format using the PACS clinical imaging

tool (Sectra PACS, version 23.1 Linköping, Sweden) and the Surgimap software (Surgimap Spine Software, version 2.3.2.1, Nemaris Inc., NewYork, NY).

3.2.2 Patient reported outcome measures

For papers I, II and III scores from the following patient reported questionnaires were used in the analyses: The Scoliosis Research Society 22r instrument (SRS-22r) [111], the EuroQol-5 dimension quality of life, three level (EQ-5D-3L) [129], the EuroQol visual analogue scale (EQ VAS) [129] and a Visual Analogue Scale (VAS) for back pain [130].

The SRS-22r is a disease-specific questionnaire developed to measure health-related quality of life in patients with adolescent idiopathic scoliosis. It has been shown to be valid and reliable in patients with adolescent idiopathic scoliosis [131]. It contains five domains: function, pain, appearance, mental health and satisfaction. A total score can be calculated by all five domains and a subscore by excluding the satisfaction domain. Domain, subscore and total score range from 1 (worst) to 5 (best) [111].

The 3-level version of the EQ-5D consists of two parts: The EQ-5D-3L descriptive system and the EQ VAS. The EQ-5D-3L descriptive system is a generic tool that measures health-related quality of life. It is consisted of five distinct dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels of severity (1 to 3) and a total of 243 different health states can be identified. A health state can then be transformed to an index score by using a scoring algorithm and this index score represents the overall quality of life and health status. The United Kingdom (UK) EQ-5D-3L value sets were used in our studies; ranging from -0.59 to 1.00, where 1.00 represents the best possible health state [129]. The EQ VAS is a visual analogue scale that ranges from 0 (worst) to 100 (best). It is a self-rated scale on which patients provide a generic assessment of their health status [129].

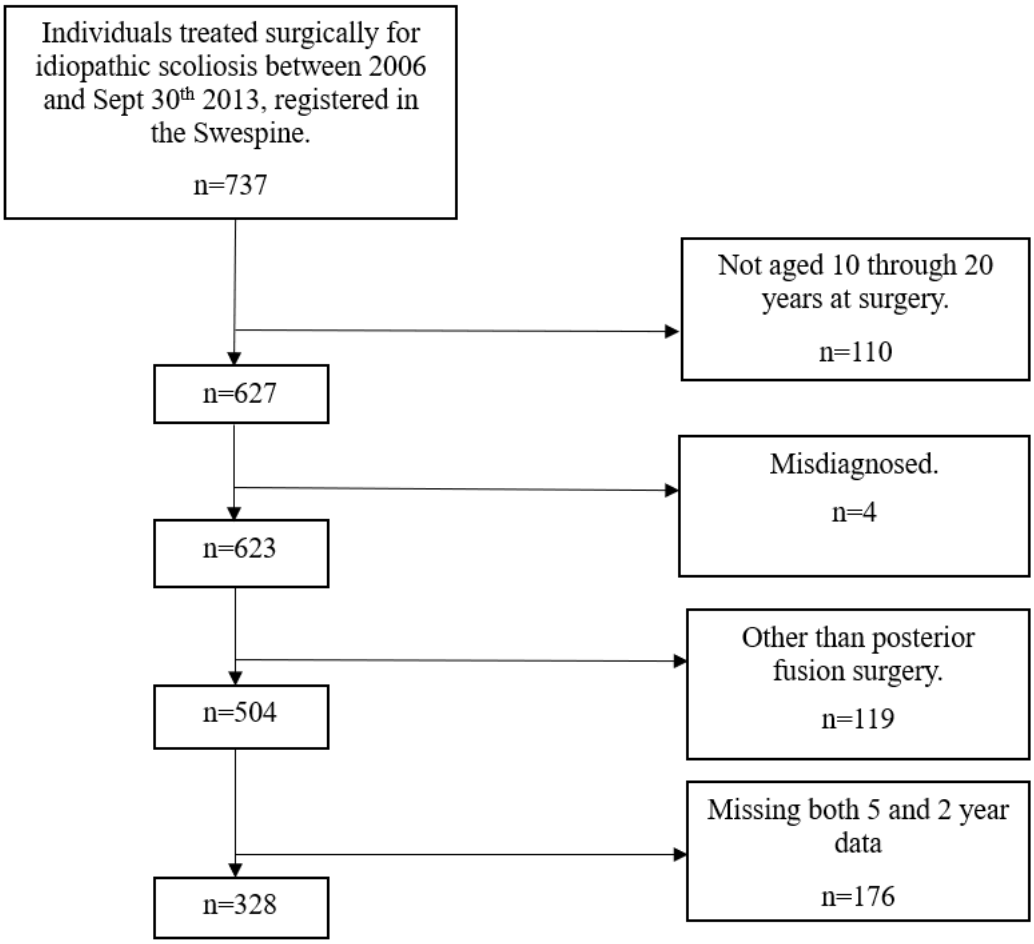
The Visual Analogue Scale (VAS) is a widely used assessment tool to measure pain intensity. It ranges from 0 (no pain) to 10 (worst possible pain) [130].

3.3 STUDY DESIGN

3.3.1 Paper I

This study was a retrospective analysis of prospectively collected data from the deformity part of the Swespine registry. The aim was to investigate whether the number of implants per operated vertebra (implant density) was associated with patient-reported outcome, correction rate of the major curve and the rate of reoperation. Three hundred twenty-eight patients, treated surgically for idiopathic scoliosis, aged between 10 and 20 years at the time of surgery were included in the analysis (*Figure 5*).

Figure 5. Flow chart for the inclusion of patients in Paper I.



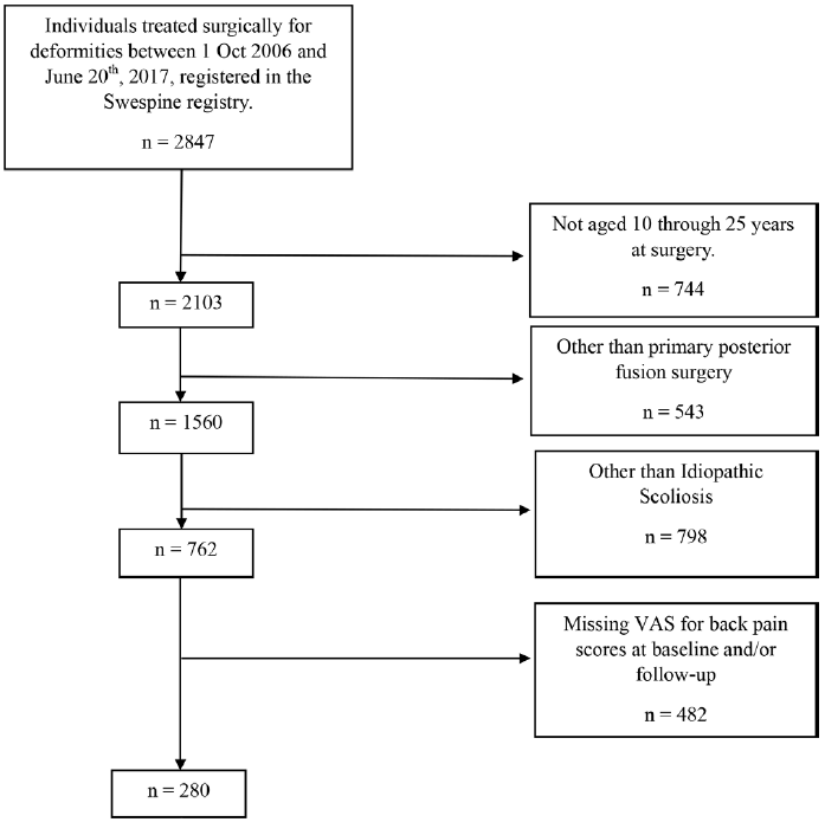
All patients had a minimum of 2-year patient-reported follow-up data. Two-year patient-reported outcome measure data were available for 210 patients and 5-year data were available for 118 patients. Preoperative, early postoperative and the last available radiographic examination of the spine were gathered from the centers where surgery was undertaken. For the analysis, patients were divided into tertiles based on their implant density. Furthermore, a subgroup of patients (n=185) with the most common type of idiopathic scoliosis (thoracic curve), was also divided into tertiles - based on implant density - for a separate analysis. Data on reoperations were searched in the registry. Due to a substantial number of patients with missing both 2-year and 5-year data (n=176), a non-response analysis was also designed in order to assess the impact of loss to follow-up on the results.

3.3.2 Paper II

The purpose of this retrospective registry-based cohort study was to identify factors that may lead to persistent postoperative pain in patients with idiopathic scoliosis treated with fusion surgery. Two hundred eighty patients (*Figure 6*) were identified in Swespine and were then divided into a high postoperative pain group (n=67) and a low postoperative pain group

(n=213) based on their reported postoperative VAS for back pain score. Forty-five mm on the 0 mm to 100 mm VAS for back pain score was used as a cut-off [132]. All patients had VAS for back pain scores at baseline and minimum of 2 years after surgery.

Figure 6. Flow chart for the inclusion of patients in Paper II.

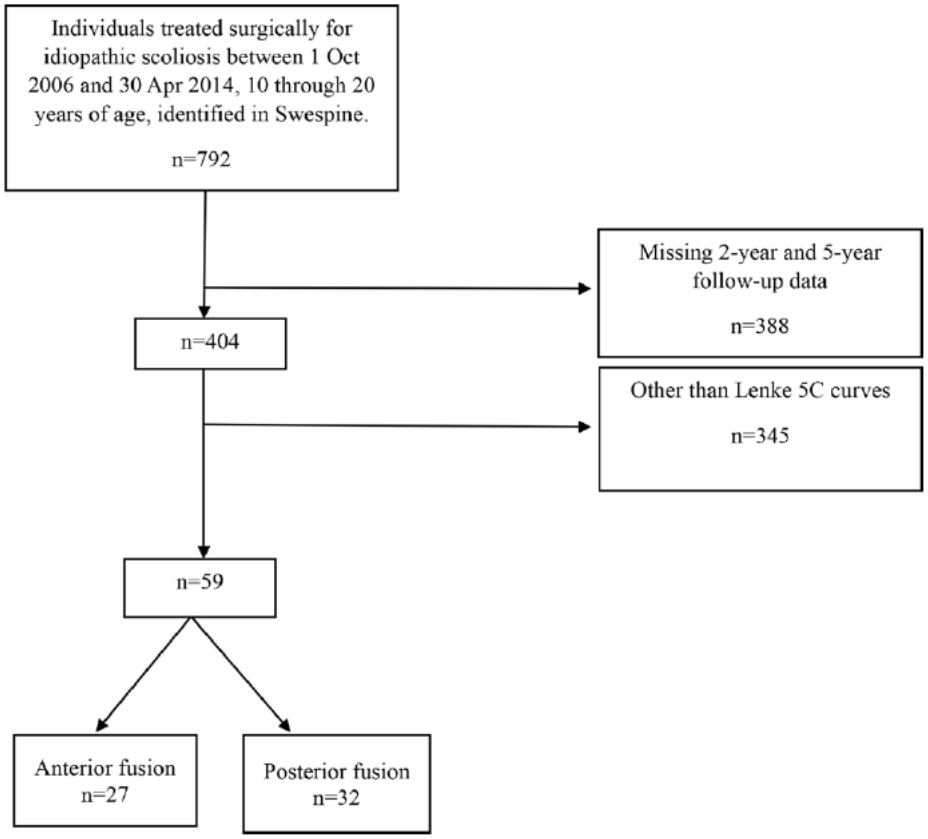


Predictors of postoperative back pain were searched in the preoperative and inpatient data registered in the Swespine.

3.3.3 Paper III

The aim of this study was to compare health-related quality of life and radiographic outcome in patients treated with fusion surgery for thoracolumbar/lumbar curve type idiopathic scoliosis, with either anterior or posterior approach. For the purpose of this study, prospectively collected data from the Swespine was used and analysed retrospectively. Fifty-nine consecutive patients (*Figure 7*) were identified and included in the analysis; 27 underwent anterior fusion surgery and 32 underwent posterior fusion surgery. All patients had preoperative and postoperative radiographic datasets and postoperative patient-reported outcome data at a minimum 2 years after surgery.

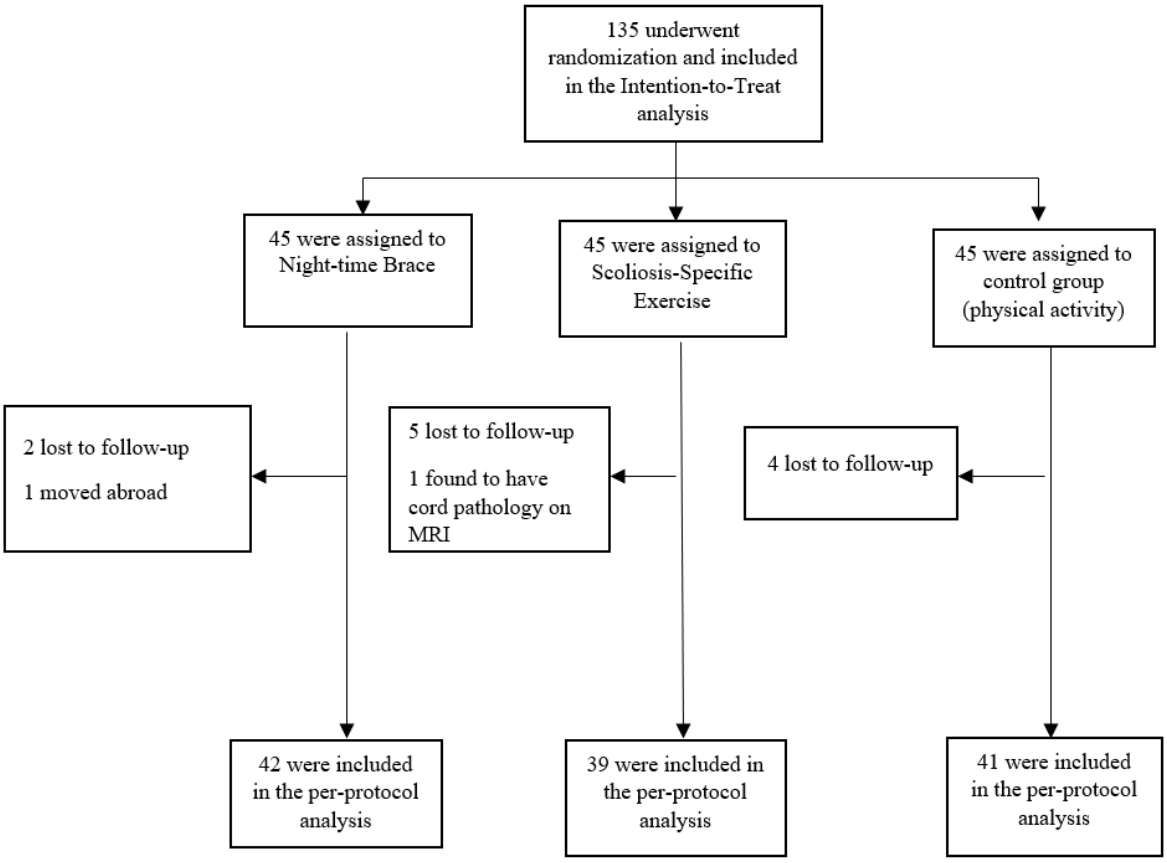
Figure 7. Flow chart for the inclusion of patients in Paper III.



3.3.4 Paper IV

The primary aim of this randomized controlled trial was to investigate on the effectiveness of night-time brace and scoliosis-specific exercise to prevent curve progression in patients with adolescent idiopathic scoliosis. The primary outcome was curve progression of 6 degrees or less by skeletal maturity, defined as treatment success, or curve progression of more than 6 degrees, defined as treatment failure. One hundred thirty-five patients were available for the intention-to-treat analysis and 122 patients were available for the per-protocol analysis (*Figure 8*). Patients who required surgical intervention due to curve progression up to 2 years post-endpoint were noted.

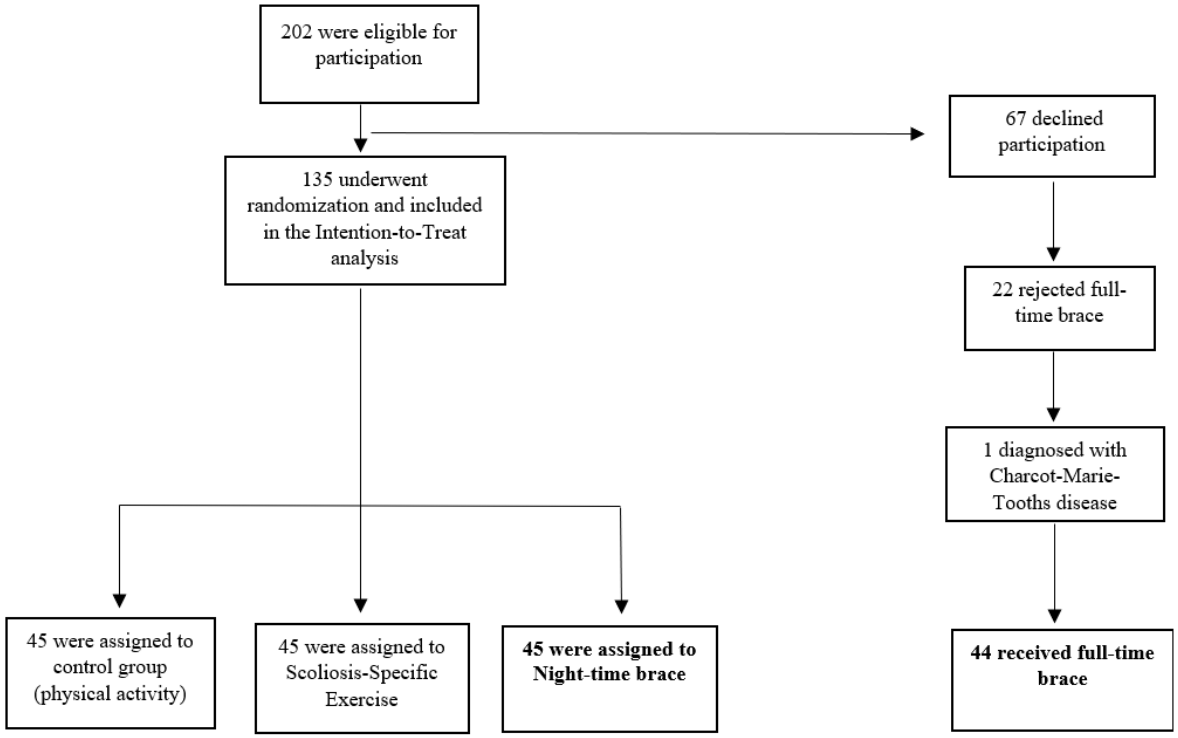
Figure 8. Flow chart for the inclusion of the patients in Paper IV.



3.3.5 Paper V

This was a retrospective analysis of prospectively collected data from the CONTRAIS trial. The aim of this study was to investigate the effectiveness of night-time brace and full-time brace on preventing curve progression in patients with adolescent idiopathic scoliosis. The hypothesis was that night-time brace would be as effective as the full-time brace to prevent curve progression of the scoliotic curve. Forty-five patients assigned to night-time brace treatment in the randomised part of the CONTRAIS trial were compared to 44 patients that had declined participation in the trial and received a full-time brace during the same time period (*Figure 9*). Patients in the night-time brace were offered transition to a full-time brace in case of curve progression of more than 6 degrees. All participants were followed clinically and radiographically until endpoint or maturity unless surgery occurred before maturity. Information on if patients had received scoliosis surgery until September 30th, 2022 was searched through patient´s medical charts and recorded.

Figure 9. Flow chart for the inclusion of the patients in Paper V.



3.4 STATISTICAL ANALYSIS

Analyses in papers I, II, III and V were conducted in SPSS versions 23-28 (IBM SPSS Statistics for windows; Armonk, New York). In paper IV, statistical analyses were conducted by an independent statistician blinded to intervention assigned to each patient participating in the study. IBM SPSS statistical software version 28 (IBM SPSS Statistics for windows; Armonk, New York), SAS system version 15.2 (SAS Institute Inc., Cary, NC, USA) and R studio statistics software, version 4.2.0 were used for the analyses. Statistical significance was set at $p<0.05$ in all analyses.

In paper I, descriptive data at baseline was presented as mean with standard deviation (+/-) and range or number and proportions (no, %). Analysis of variance (ANOVA), Pearson´s Chi-square test or the Fisher exact were used for group comparisons. Variables that differed significantly at baseline (gender, age at the time of surgery, flexibility of the major curve and follow-up time) were entered as covariates in the analysis of covariance (ANCOVA). For within group comparisons, two-tailed paired Student´s t-test was conducted. Kaplan Meier analysis and log rank test were used to estimate differences in the proportion of the patients without a revision surgery in the groups. In case of missing data, exclusions were made analysis by analysis.

In paper II, descriptive statistics were presented as mean with standard deviation (+/-) or number and proportions (no, %). The cohort was divided into a “high pain group” and a “low pain group” by using the 45mm on the VAS scale as a cut off. Analysis of variance (ANOVA)

was performed for group comparisons. A two tailed paired sample t-test was used for within group comparisons. For categorical data, group comparisons were conducted by using the Pearson´s Chi-square test or the Fisher exact test. Variables that significantly diffed at baseline (sex, VAS back pain, EQ VAS, SRS-22r function, SRS-22r pain, SRS-22r self-image, SRS-22r mental health) were identified as risk factors for postoperative pain in a logistic regression model. The same variables were then entered in forward stepwise selection in a binary logistic regression model. Exclusions were made analysis by analysis, in case of missing data.

In paper III, descriptive data was presented as mean with standard deviation (+/-) or number and proportions (no, %). Independent samples t-test and analysis of variance (ANOVA) were used for group comparisons. A two tailed paired sample t-test was used for within the group comparisons. Confounding variables at baseline (sex, age at surgery and number of fused vertebrae) were entered as covariates in the analysis of covariance (ANCOVA).

In paper IV, a power analysis was conducted before the start of the trial to determine the minimum sample size required for the study. Based on previous studies in the literature, a failure rate of 15% was set for the night-time brace and the scoliosis-specific exercise groups and a failure rate of 45% was set for the self-mediated physical activity group. The dropout rate was set at 20%. Thus, 135 patients – 45 in each group – would be required to have 80% power to detect differences between the groups at a significance level of 5%. Inter-rater reliability was performed to measure the degree of agreement between: 1) the two blinded assessors who conducted all the radiographic measurements after the end of the study and 2) the health-care providers who conducted radiographic measurements during the study period and the two blinded assessors. For the former, measurements on the Cobb angle of the major curve at baseline were used for the analysis. For the latter, measurements on the Cobb angle of the major curve at baseline and at the end of the study were used. A two-way mixed effects model was used to calculate the intraclass correlation coefficient (ICC) ranging between 0 and 1. Values below 0.5 indicate poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and any value above 0.9 indicates excellent reliability [133]. The primary analysis was an intention-to-treat. In this analysis, estimates on treatment effect were calculated for the entire population in each group, regardless of drop-out, loss to follow-up or non-compliance. Practitioner-reported patient adherence to the treatment protocol was dichotomized into “very high grade and high grade” or “low grade and not at all” for each 6 monthly follow-up until endpoint. An ITT analysis weighted for treatment adherence and a complete case per-protocol analysis weighted for treatment adherence was then conducted. Categorical variables were compared by the Pearson´s Chi-square test or the Fisher exact test. For continuous variables, analysis of variance (ANOVA) with Dunnett´s correction was conducted for group comparisons. Kaplan-Meier survival analysis and pooled logistic regression were performed to estimate the hazard ratio probability of curve survival of 6 degrees or less over time for each group. Each analysis was adjusted for baseline covariates (age, Risser stage, Cobb angle of the major curve, gender).

In paper V, baseline descriptive statistics were presented as mean with standard deviation (+/), number and proportions (no, %) or median with interquartile range (IQR). Quantile – Quantile (Q-Q) scatterplots were used to assess data distribution. Independent samples t-test was used for group comparisons of continuous variables. Non-normally distributed data was analyzed by the Mann-Whitney U-test. Categorical variables were compared by the Pearson´s Chi-square test or the Fisher exact test. A binary logistic regression was conducted to estimate the odds ratio of major curve progression to ≥ 45 degrees at the last available radiographic follow-up. Covariates entered in the regression model were decided a priori. These included: Age, gender, curve size at the beginning of brace treatment, in-brace correction, menarcheal status (for girls) and Risser grade.

3.5 ETHICS

Ethical approval was obtained for all research projects included in this thesis and detailed information can be found in each paper separately.

In the randomized controlled trial, we followed all international and scientific quality requirements needed for trials that involve human subjects. All patients who fulfilled the inclusion criteria were invited to participate, regardless of researchers´ beliefs on the appropriate treatment. Patients who could consider participation in the study were given detailed written information about the randomization process, the interventions and the follow-up. Participation was voluntary and all patients had the right to withdraw from the trial at any time. Additionally, patients in the trial were offered a closer radiographic follow-up compared to standard treatment. Hence, patient safety was insured since progression of the scoliosis was captured on early stages and patients were then offered transition to a full-time brace.

Nevertheless, there are some ethical considerations that need to be pointed out. During the course of this trial, new evidence based on prospective studies highlighted the benefit of bracing in the conservative treatment of idiopathic scoliosis. Thus, our choice to continue this trial may be criticized. However, before inclusion all patients were informed that the standard of care - at that point in time- was the full-time brace, based on the current literature. Our impression was that patients who chose to participate in the study were those not willing to accept a full-time brace. Our perspective was that further research was needed in order to improve evidence on brace and scoliosis-specific exercise treatments in idiopathic scoliosis. This was also supported by the conclusions of a feasibility study on future RCTs and a Cochrane review published in 2015 [134, 135].

4 RESULTS

4.1 PAPER I

In total, 6045 implants were used in the entire cohort. The majority were pedicle screws (94%). The mean implant density in the low, medium and high-density groups was 1.36 (*range:* 1.00 to 1.54), 1.65 (1.55 to 1.75) and 1.91 (1.77 to 2.00), respectively. The mean postoperative clinical follow-up time was 3.1 years, the mean radiographic follow-up time was 1.9 years and the mean time to reoperation was 5.5 years.

At baseline, patients in the high implant density group were significantly older at the time of surgery (15.6, 15.9 and 16.3 respectively, p=0.042) and demonstrated less flexible scoliotic curves (23%, 24% and 22% respectively, p=0.027). Furthermore, there was a lower proportion of females in the high implant density group (86%, 84% and 72% respectively, p=0.014). All other preoperative characteristics, patient reported and inpatient data did not differ significantly between the three implant density groups (all $p \geq 0.09$), except for a significantly higher perioperative blood loss in the high implant density group (1044 ml, 1069 ml, and 1338 ml respectively, p=0.020).

At the one-year follow-up, comparisons between the three implant density groups (adjusted for gender, age at the time of surgery, and major curve flexibility) revealed a statistically significantly higher SRS-22r score for satisfaction in the high implant density group (4.1, 4.2 and 4.5 respectively, p=0.013). Overall, there were no other significant differences in patient-reported outcome scores between the three implant density groups (all $p \geq 0.08$).

At the mean 3.1-year follow-up, analyses were also adjusted for follow up time due to a shorter follow-up time in the high implant density (3.1 years in the low, 3.3 years in the medium and 2.7 years in the high implant density group). Comparisons between the three implant density groups showed a statistically significantly higher SRS-22r satisfaction score in the high implant density group (4.0, 4.3 and 4.3 respectively, p=0.034) and a statistically significantly higher SRS-22r self-image score in the medium implant density group (3.8, 4.0 and 3.9 respectively, p=0.029). Subanalysis of patients with the most common type of scoliosis (main thoracic curves) did not show significant differences in patient-reported outcome scores between the three implant density groups (all $p \geq 0.12$).

In total, 24 (7.3%) patients underwent revision surgery at the mean follow-up of 5.5 years after index surgery. Survival analysis showed no significant difference in the number of patients who did not require revision surgery (p=0.45).

The non-response analysis showed statistically significantly lower scores for non-responders in SRS-22r function (4.1 versus 4.4, $p<0.002$) and SRS-22r subscore (3.6 versus 3.8, p=0.042).

4.2 PAPER II

Baseline characteristics did not differ significantly between the low and the high postoperative pain group (all $p \geq 0.05$), except for a higher proportion of females in the high postoperative pain group ($p=0.028$). When comparing baseline self-reported data at baseline, patients in the high postoperative pain group reported significantly higher VAS for back pain scores, lower EQ VAS scores and significantly lower SRS-22r domain scores and subscores (all $p \leq 0.039$).

At the mean 3-year follow-up, comparisons between the low and the high postoperative pain group showed significantly lower EQ-5D-3L index, lower EQ VAS and SRS-22r scores (all domains, subscore and total score) in the high postoperative pain group (all $p < 0.001$). Moreover, when compared to preoperative, patients in the high postoperative pain group, reported a significant worsening of their status with increased VAS for back pain scores, decreased EQ-5D-3L index, decreased EQ VAS and SRS-22r pain scores (all $p \leq 0.037$). On the other hand, patients in the low postoperative pain group experienced a significant positive change in all postoperative scores (all $p<0.001$) except for the SRS-22r mental health score ($p=0.3$).

In the regression analysis, preoperative VAS for back pain and preoperative SRS-22r mental health were found to be predictors of postoperative back pain. Patients with increased VAS for back pain scores before surgery had a higher risk of being in the high postoperative back pain group (odds ratio [OR] 1.03; 95% CI 1.02 to 1.05 per mm increase on the VAS scale). Patients with low SRS-22r mental health scores preoperatively had a higher risk of being in the high postoperative back pain group (OR 1.68; 95% CI 1.03 to 2.73 per point decrease on the preoperative SRS-22r mental health score).

In total, 20 (7%) patients underwent revision surgery at a mean of 2.7 years after the primary scoliosis surgery. There was a significantly higher number of revision cases in the high postoperative pain group compared to the low postoperative pain group (9 out of 67 versus 11 out of 213 cases respectively, $p=0.030$). When compared to patients who did not undergo revision surgery, patients who underwent revision surgery reported significantly higher VAS for back pain scores, lower EQ-5D-3L, lower SRS-22r satisfaction scores and SRS-22r subscores and total scores (all $p \leq 0.042$) at the mean 2.7 years after index surgery.

4.3 PAPER III

Baseline characteristics were similar between the anterior and the posterior fusion surgery group (all $p \geq 0.5$). Similarly, there were no significant radiographic differences in terms of magnitude of the major curve, curve flexibility and sagittal parameters (all $p \geq 0.2$).

Perioperative data showed that there was a significantly higher blood loss (705 ml [617] versus 324 ml [276] respectively, $p=0.004$), significantly higher number of fused vertebrae (9 [3] versus 5 [1] respectively, $p<0.001$) and a significantly higher number of implants (16 [5] versus 10 [1] respectively, $p<0.001$) in the posterior fusion group. Implant density did not differ between the anterior and the posterior fusion group ($p>0.05$). Duration of surgery was

significantly longer in the anterior fusion group (272 min [83] versus 182 min [89] respectively, p<0.001).

At mean 3.8 years after the index surgery, there were no significant differences in the SRS-22r scores, EQ-5D-3L, EQ VAS and VAS for back pain scores (all p≥0.2, adjusted for sex, age at surgery and number of fused vertebrae).

Compared to baseline, there was a significant reduction of the magnitude of the major curve both in the anterior (48 [7] versus 17 [10], p<0.001) and the posterior fusion group (48 [10] versus 17 [9], p<0.001). There were no significant postoperative differences in terms of curve correction or sagittal parameters between the anterior and the posterior fusion group (all p≥0.4). Posterior fusion surgery was significantly associated with longer constructs; in 65% of the constructs, the upper instrumented vertebra was above the level of the 10^{th} thoracic vertebra, while in the anterior group the most cranial instrumented vertebra was the 10^{th} thoracic vertebra (26%) and the most common one was the 11^{th} thoracic vertebra (52%). However, longer constructs were not associated with any significant difference in patient-reported outcome measures (p≥0.3).

A total of 8 (14%) patients underwent revision surgery at a mean of 16 months after the primary fusion surgery. Analysis showed no significant difference in the reoperation rate between the anterior and the posterior fusion group (p=0.3).

4.4 PAPER IV

The mean age at inclusion was 12.7 (1.4), and 111 of the participants in the trial were females (82%). Baseline characteristics were similar and homogeneous in the 3 groups. The intraclass correlation coefficient (ICC) showed `good´ reliability for the two independent raters (0.86 [95 % CI: 0.79 to 0.89]). The ICC between the two independent raters and the healthcare providers who conducted all measurements during the study period showed excellent reliability on both timepoints: at baseline (0.91 [95 % CI: 0.87 to 0.93]) and at the end of the study (0.96 [95 % CI: 0.94 to 0.97]).

In the intention-to-treat analysis, there was a significantly higher success rate in the night-time brace group compared to the self-mediated physical activity group (76% versus 53%, p=0.028). Patients in the night-time brace group remained significantly longer in the study compared to patients in the self-mediated physical activity group (22.8 [12.9] months versus 16.2 [10.5] months respectively, p=0.012). The odds ratio (unadjusted) for successful outcome with the night-time brace was 2.7; 95% CI, 1.1 to 6.6, compared to self-mediated physical activity. On the other hand, there was no significantly higher success rate in the scoliosis-specific exercise group when compared to the self-mediated physical activity group (58% vs 53%; (1.2 [95 % CI: 0.5 to 2.8]), p=0.67).

Thirteen patients (10%) dropped out of the study due to the following reasons: 11 patients were lost to follow-up; 1 patient moved abroad; 1 patient found with cord pathology (Chiari with syringomyelia) on magnetic resonance imaging (MRI). There were no significant differences

in the dropout rates between the three groups (p=0.3). Thus, 122 participants remained for the per-protocol analysis: 42 in the night-time brace group, 39 in the scoliosis-specific exercise group and 41 in the self-mediated physical activity group. The results of this analysis showed that there was a significantly higher success rate in favor of the night-time brace (74% vs 49%; p=0.019). Patients in the night-time brace group remained significantly longer in the study compared to patients in the self-mediated physical activity group (24.1 [12.3] months versus 17.2 [10] respectively, p=0.007). On the other hand, there was no significantly higher success rate in the scoliosis-specific exercise group when compared to the self-mediated physical activity group (51% vs 49%; p=0.82).

Intention to treat analyses weighted for treatment adherence and adjusted for baseline covariates revealed that had everyone been assigned to night-time brace, the hazard of progress would be 0.16 (95% CI, 0.05 to 0.52) times the hazard of progress had everyone been assigned to self-mediated physical activity only, over the 6 monthly follow-up periods until endpoint (p=0.002). Had everyone been assigned to scoliosis-specific exercise, the hazard of progress would be 0.58 (95% CI, 0.20 to 1.63) times the hazard of progress had everyone been assigned to self-mediated physical activity only, over the 6 monthly follow-up periods until endpoint (p=0.3).

Survival analysis showed a statistically significant difference in the probability of successful treatment with the night-time brace compared to self-mediated physical activity (log rank=7.3, p=0.007).

In total 27 (18.5%) patients required fusion surgery within 2 years post-endpoint due to progression of the scoliosis into the surgical magnitude. However, there were no significant differences in the operation rates between the groups (9 patients in each group, p=0.7).

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The median age at brace start was 12.8 (IQR:1.8) years; the median follow-up time was 33 months (IQR:26).

Comparisons for baseline characteristics between the night-time brace and the full-time brace did not show significant differences (all p≥0.1), except for a greater angle of trunk rotation in the night-time brace group (11 [IQR:4] versus 10 [IQR:5] respectively, p=0.03). Radiographically, the night-time brace group demonstrated a greater lumbar lordosis compared to the full-time brace group (-50 [15] versus -48 [9] respectively, p=0.021). All other radiographic parameters concerning the location and magnitude of the major curve, thoracic kyphosis and percentage of in brace correction of the major curve did not differ significantly between the 2 groups (all p≥0.06).

The median follow-up time from brace start until the last available radiographic control did not differ significantly between the night-time brace and the full-time brace group (33 [IQR:24] months versus 33 [IQR:27] months respectively, p=0.9); neither the magnitude of the major curve measured according to the Cobb method (39 [11] versus 38 [11] respectively, p=0.7).

Regarding curve progression into the surgical magnitude, 16 patients in the night-time brace group and 14 patients in the full-time group demonstrated curve progression to ≥ 45 degrees at the last available radiograph (p=0.7). In terms of surgical intervention, 11 patients in the night-time brace group and 6 in the full-time brace group underwent fusion surgery (OR 2.0; 95% CI 0.7 to 6.1). Female gender (OR 6.5; 95% CI 1.12 to 37.38), lower Risser grade (OR 1.6; 95% CI 1.01 to 2.67) and larger curve size at brace start (OR 0.7; 95% CI 0.65 to 0.87) were independently associated with higher likelihood of curve progression ≥ 45 degrees.

5 DISCUSSION

5.1 GENERAL DISCUSSION

This thesis includes the first fully randomized controlled trial on the effectiveness of night-time brace and scoliosis-specific exercise to prevent curve progression in patients with adolescent idiopathic scoliosis. The ultimate goal of treatment in patients with idiopathic scoliosis, is to stop progression of the deformity and subsequently reduce the risk of surgery. This is of considerable importance, since in patients who underwent surgery for scoliosis, quality of life has been found to be reduced when compared to quality of life in the general population [136].

The major finding of this trial was that night-time brace reduced the progression of the scoliosis in 3 out of 4 patients. We found a significantly higher success rate when patients in the night-time brace were compared to patients who only conducted self-mediated physical activity (76% versus 53%). Previous studies on the effectiveness of braces, were mainly focused on full-time braces. Nachemson et al. in a prospective non-randomized trial also known as the ¨SRS brace study¨, reported significanlty higher success rate in the prevention of curve progression with the brace in 286 girls with idiopathic scoliosis treated with either a brace (n=111) or observation only (n=129) or night-time electrical stimulation (n=46) [137]. Since then, several attempts have been made for randomized controlled studies in an effort to improve the current evidence. However, these have either failed to include patients in the trials [138, 139] or started as a randomized trial and during the course of the study changed to include a preference cohort [86]. Nevertheless, in all these studies – with the exception of one which only included 4 patients [140] – full-time braces were associated with a positive outcome in terms of effectiveness of the brace to prevent curve progression when compared to observation only. Due to a need for high quality studies in the field, we decided to conduct a trial on the night-time brace since its effectiveness had never been tested in a controlled setting and current evidence was only based on studies retrospective in nature. Success rates to prevent curve progression in these studies ranged between 52% and 89% [90, 141-144], similar to the success rate we observed in this trial.

In contrast to what we observed with the night-time brace, scoliosis-specific exercise did not result in a higher success rate when compared to self-mediated physical activity. While interest in scoliosis-specific exercise as a treatment method for idiopathic scoliosis has been growing over the last years, its effectiveness has been unclear. In cases of mild idiopathic scoliosis (less than 25 degrees of Cobb angle), there has been one randomized trial available in the literature; Monticone et al. assigned 110 individuals with adolescent idiopathic scoliosis to either an active self-correction scoliosis-oriented training program (n=55) or to traditional exercises (n=55). They found that the scoliosis oriented rehabilitation program improved the scoliotic curve significantly while patients in the traditional training group remained stable. The effects of the intervention were measured at skeletal maturity and at the 12 month follow-up [81]. In moderate (25 to 40 degrees of Cobb angle) idiopathic scoliosis, there have been several randomized controlled trials investigating the effectiveness of physiotherapeutic scoliosis-

specific exercise either compared to full-time brace or as an add-on to full-time bracing. Zheng et al. randomly assigned 24 patients in full-time brace treatment and 29 in a scoliosis-specific exercise program. They reported superiority of the brace to reduce the magnitude of the curve over a 12 month follow-up [145]. Similar results were reported in another randomized trial by Yagci et al. However, this trial suffered by a small number of participants (15 in each group) and the lack of a control group. Moreover, estimates of treatment effect were measured only at one timepoint, 4 months after the start of the intervention and not at skeletal maturity or beyond [146]. Schreiber et al. investigated on the effectiveness of Schroth scoliosis exersice protocol added to standard of care (observation or brace treatment) and found greater reduction of the curve when Schroth exersices were used as an add-on to the standart care of treatment. However, this trial was limited by a short follow-up, heterogenous sample size due to wide inclusion criteria and limited statistical power due to early termination of the study [147]. Therefore, a recently published systematic review concluded that there is insufficient evidence to draw firm conclusions on the effectiveness of scoliosis-specific exercice in adolescent idiopathic scoliosis [148]. To our knowledge, the current trial was the first one designed to include an active control group in the randomization process.

While full-time braces have been the standard of care in brace candidates with idiopathic scoliosis, the use of night-time braces has also evolved over the last decades. The main argument for its use has been the limited amount of time a night-time brace needs to be worn; during the night. Hence, the psychological and funtional impact of all-day brace on daily life could be minimized. When we compared night-time braced patients from the randomized arm of the trial to patients who received the standard of care consisted of a full-time brace, we found similar effectiveness between the two brace types to prevent curve progression. The higher number of surgeries in the night-time brace group compared to the full-time brace group is of some concern, even though this difference did not reach statistical significance. A future study with longer follow-up may elucidate that part. Similar results were reported in previous observational studies. Gepstein et al. conducted a retrospective analysis of 122 patients with idiopathic scoliosis, treated with either a Charleston night-time brace (n=87) or a full-time brace (n=37). Both treatment options were found similar effective to prevent curve progression. However, their study did not follow the Scoliosis Research Society (SRS) and the International Society on Scoliosis Orthopedic and Rehabilitation Treatment (SOSORT) criteria [149]. In keeping with Gepstein et al. were the results reported by Ohrt-Nissen et al.; the investigators found no difference in curve progression between idiopathic scoliosis patients treated with either a Boston full-time brace (n=37) or a providence night-time brace (n=40). However, in their analysis they included only patients with a main thoracic type scoliosis [90]. More recently, a published metanalysis and a systematic review based on SRS criteria reported similar effectiveness of night-time and full-time braces for the conservative treatment of patients with idiopathic scoliosis [150, 151]. Our findings contribute significantly to the existing evidence. Based on our and others results, night-time braces can be suggested as an alternative method of treatment in patients with adolescent idiopathic scoliosis.

Despite the fact that braces seem to prevent progression of idiopathic scoliosis, there are always cases unresponsive to treatment where conservative treatment fails; the curve progresses to a magnitude where surgery can be recommended. Although new promising techniques such as minimally invasive with navigation or robotic asssisted surgery have emerged over the last years, open surgery is still the most prevalent method of treatment. According to several studies, posterior based fixation techniques, especially after the introduction of pedicle screws, have made it feasible to achieve great correction rates, similar to anterior based techniques dominated in the past. In a cohort of 59 idiopathic scoliosis patients treated with either anterior (n=27) or posterior (n=32) fusion surgery for a thoracolumbar/lumbar type curve, we found similar correction rate and quality of life after surgery. Anterior fusion surgery was associated with longer operative time while posterior fusion surgery was associated with higher blood loss and longer constructs. Our results are consistent with previous reports in the literature. Recently, Miyanji et al. compared 161 consecutive idiopathic scoliosis patients treated with either anterior (n=69) or posterior (n=92) instrumented fusion for thoracolumbar/lumbrar type scoliosis. At the 2-year follow-up, the authors found no difference in the percentage of curve correction and patient reported outcome scores between the anterior and posterior fusion groups. Anterior surgery was associated with shorter fusion constructs [152]. Several other studies reported similar results [153, 154]. Hence, either of the two approaches can be suggested for the surgical treament of patients with thoracolumbar/lumbar type of idiopathic scoliosis.

Over the past decades, pedicle screw constructs have become the state-of-the art instrumentation for surgical treatment of adolescent idiopathic scoliosis. A number of studies have shown advantages of pedicle screws over traditional ways of fixation with hooks or hybrid constructs. However, there has been no consencus on the ideal number of implants to be used per vertebra (implant denisty) for the correction of scoliosis and many authors have advocated higher implant density for better curve correction. Moreover, whether implant density has an influence on clinical outcome is still a subject of debate. Our results showed that implant density is not related to the correction rate of scoliosis, patient-reported outcome and reoperation rate. Although we divided our cohort into a low, medium and high implant density group in an effort to capture differences with different implant density constructs, we still found similar radiographic and clinical outcomes without differences in the reoperation rates over a long period of time after index surgery. Similar to our results, several studies reported no correlation between implant density, curve correction and patient-reported outcome [155-157]. To date one well-designed multicenter randomized controlled trial is ongoing; preliminary results presented at an international congress showed no difference in the percentage of coronal correction in patients with idiopathic scoliosis assigned to either high (>1.8 screws per level fused) or low (<1.4 screws per level fused) implant density [158, 159]. The final results of this study are expected in the near future. In summary, there is a growing body of evidence suggesting that a higher number of implants is not necessary in the surgical treatment of idiopathic scoliosis.

While surgery for idiopathic scoliosis has been associated with improvents in self-reported quality of life and satisfaction, there are patients who experience persistent back pain and dissatisfaction after surgery. Studies have shown that a satisfactory radiographic outcome is poorly correlated to clinical outcome from a patient´s point of view. Therefore, identifying factors associated with poor clinical outcome is truly crucial, since these may be used as a tool for patient information on the outcome after scoliosis surgery and at the same time support healthcare providers in developing stategies and best practices to meet patient expectations. In our analysis, we found that roughly 1 out of 5 patients experienced significant and persistent back pain long after the scoliosis surgery. Compared to patients with low postoperative pain, patients in the high postoperative group reported high levels of pain and lower quality of life before surgery. Although the majority reported a significant improvent of their back pain and quality of life after surgery, patients with peristent postoperative pain reported worsening of their back pain and quality of life compared to before surgery. High levels of back pain and low mental health before surgery were associated with high levels of back pain after surgery. Overall, the association between high levels of pain before surgery and greater incidence of postoperative pain has been verified in the literature. Connelly et al. identified higher levels of pain and anxiety before surgery as risk factors for chronic postoperative pain [160]. However, the small size of this cohort and the short follow-up may have limited this study. In line with Connelly et al. were the results reported by Hwang et al. In a retrospective analysis of 1744 surgically treated idiopathic scoliosis patients with a minumum of 2 year follow-up, they identified high preoperative pain as the primary predictor of increased pain after surgery [161]. Using data from the same registry, they also found low mental health before surgery to be associated with high levels of preoperative pain [162]. In summary, our results demonstrated that pain after surgery for idiopathic scoliosis may be prevalent in patients with high levels of pain before surgery.

5.2 STRENGTHS AND LIMITATIONS

In this thesis we present the results of the first fully randomized controlled trial on the effectiveness of two different modalities, night-time brace and scoliosis-specific exerscise, for the conservative treatment of adolescent idiopathic scoliosis. Previous efforts for similar studies have either failed to include participants or ended up early, reflecting the difficulties in the conduction of this type of studies. Our well defined inclusion criteria based on international guidelines and recommendations, the multicenter nature, the true randomization and the blind assessment of the outocomes were key components to ensure quality in the conduction and outcome interpretation of this trial.

There are also limitiations in this trial. In a highly controlled setting, one may critisize our results as generally not applicable. However, our findings are supported by previous high quality studies, giving external validity to our results [86, 137].The content of the scoliosis-specific exercise intervention may also be critisized, since we synthesized a broad exercise treament protocol without any preference to a specific treatment regime. However, the synthesis of this protocol was based on the best available evidence at the time we designed the study with the aim to be applicable on an outpatient setting. We did not use objective measures

for patient compliance and our estimates were based on self-report. While overstimated self-reported compliance can be expected [163, 164], we do not believe that it had an impact on our results on the effectiveness of the interventions, since compliers and non compliers should be equally distributed in a controlled setting. Transition to a full-time brace in cases of curve progression may have had an impact on the true treatment effect of the interventions. Finally, double blinding was not feasible in the current trial owing to the nature of the interventions.

A part of this thesis includes observational studies based on data from a prospective nationwide quality registry, the Swespine. The use of large cohorts, validated outcome instruments and longer follow-up in combination with Swespine´s high coverage, completeness and diagnostic accuracy, gives high external validity to our results [123, 124].

Nevertheless, there are certainly limitations related to the retrospective nature of these studies. Selection bias is a common drawback in all observational cohort studies. However, the large and nationwide sample sizes compensate for this limitation, giving to our results high external validity. Despite our large sample sizes, loss to follow-up was also observed and could skew our results and conclusions on treatment effects. However, a recent study showed that loss to follow-up in Swespine has minor effect on the results [124]. Thus, we assume that, non-response in our studies did not have a major effect on outcome interpretation. Finally, in all our observational studies, we used the EQ-5D-3L as a non-specific quality of life instrument, even though a youth version, the EQ-5D-3L-Y, has been introduced recently [165]. Nevertheless, in a recently published study, the use of EQ-5D-3L in younger individuals resulted in similar scores compared to EQ-5D-Y in Swedish adolescents from the general population, indicating that EQ-5D-3L may be used in a younger population [166].

POINTS OF PERSPECTIVE

The findings presented in this thesis may have direct clinical implications since we provide evidence on the effectiveness of night-time brace to reduce curve progression in patients with adolescent idiopathic scoliosis. Our findings may help healthcare providers to improve treatment protocols and practices in the conservative treatment of patients with idiopathic scoliosis.

Back pain may be present in patients treated surgically for idiopathic scoliosis and future studies and directions should focus on preventive strategies in a multidisciplinary fashion.

With the introduction of modern techniques and new fixation systems the cost of scoliosis surgery has increased. Using low implant density constructs without compromising outcomes may reduce the costs. This is of crucial importance especially in a public healthcare setting. Future studies on cost-effectiveness could highlight that part.

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