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Ella Virkki

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To my Mom and Dad

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ABSTRACT

Spondylolysis is the most common cause of low back pain in adolescents, explaining up to 47% of low back pain in young athletes. It is a stress fracture in one or both of the pars interarticularis of the vertebra, most likely seen in the L5 vertebra. If spondylolysis is bilateral and does not achieve bony union after treatment, it can lead to spondylolisthesis, which means a forward slippage of the vertebral body compared to the vertebral body below it.

Treatment of pediatric spondylolysis consists of restriction of sports, physical therapy, and in some instances a brace treatment. Usually, the treatment time is around three months. The goal of the treatment is bony union of the fracture, resolution of symptoms, and the return of a young athlete to previous activity level.

In this study, we aimed to examine whether an individual, custom-made, hard thoracolumbosacral orthosis (Boston brace) adds the likelihood of achieving bony union for spondylolysis. We wanted to discover the predictive factors for bony healing of spondylolysis. Our other interest was the health-related quality of life (HRQoL) of spondylolysis patients before and after treatment with different brace types. The last goal of this study was to evaluate the HRQoL of the operatively treated spondylolisthesis patients and whether it reaches the same level as that of age and gender matched controls.

This study shows that a customized, rigid thoracolumbosacral orthosis does not increase the likelihood of bony union of spondylolysis when compared to a low-profile, elastic lumbar support. We established that unilaterality, an early stage of spondylolysis in CT, an incomplete fracture in MRI, and a high signal intake in MRI are predictive factors for bony union of the spondylolysis. The HRQoL of spondylolysis patients at the end of the treatment is similar with different treatments. The HRQoL of operatively treated spondylolisthesis patients improves postoperatively but remains at a lower level when compared to healthy controls.

KEYWORDS: spondylolysis, spondylolisthesis, brace treatment, adolescents, health-related quality of life

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TIIVISTELMÄ

Spondylolyysi eli nikamakaaren höltymä on yksi yleisimmistä alaselkäkivun aiheuttajista nuoruusiässä, ja se selittää jopa 47 % nuorten urheilijoiden alaselkäkivusta. Se on rasitusmurtuma, joka syntyy nikaman yhteen tai kumpaankin pars interarticularikseen ja on yleisin L5-nikamassa. Jos spondylolyysi on molemminpuolinen eikä luudu hoidon myötä, se voi johtaa spondylolisteesiin. Spondylolisteesillä tarkoitetaan nikamasolmun liukumista eteenpäin suhteessa alapuolella olevaan nikamasolmuun.

Lasten spondylolyysin hoitona käytetään liikuntakieltoa, fysioterapiaa ja joissain keskuksissa korsettihoitoa. Tavallinen hoitoaika on noin kolme kuukautta. Hoidon tavoitteena on murtuman luutuminen, oireiden lievittyminen ja nuoren urheilijan paluu aiemmalle aktiivisuustasolle.

Tässä tutkimuksessa tavoitteenamme oli tutkia yksilöllisen, mittatilauksena tehdyn kovan korsetin (Boston brace) vaikutusta spondylolyysin luutumiseen. Lisäksi halusimme selvittää, mitkä tekijät ennustavat murtuman luutumista. Olimme myös kiinnostuneita spondylolyysipotilaiden elämänlaadusta ennen hoitoa ja hoidon jälkeen sekä siitä, vaikuttaako hoitomuoto elämänlaatuun. Viimeisenä tavoitteena oli selvittää leikattujen spondylolisteesipotilaiden elämänlaatua ja arvioida, saavuttaako se terveiden verrokkien kanssa saman tason.

Tämä tutkimus osoittaa, että yksilöllinen kova korsetti ei lisää spondylolyysin luutumistodennäköisyyttä, kun sitä verrataan hoitoon pehmeällä tukiliivillä. Murtuman yksipuolisuus, tuoreus MRI-/CT-kuvissa ja signaalilisä MRI-kuvissa ovat luutumista ennustavia tekijöitä. Spondylolyysipotilaiden elämänlaatu hoidon päättyessä on sama riippumatta siitä, millaisella korsetilla potilasta hoidettiin. Leikattujen spondylolisteesipotilaiden elämänlaatu kohenee leikkauksen myötä, mutta ei saavuta samaa tasoa kuin terveiden verrokkien elämänlaatu.

AVAINSANAT: spondylolyysi, spondylolisteesi, korsettihoito, nuoret, elämänlaatu

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Central Abbreviations

AIS	Adolescent idiopathic scoliosis
ANOVA	Analysis of variance
CI	Confidence interval
CT	Computed tomography
HRQoL	Health-related quality of life
LIPUS	Low-intensity pulsed ultrasound
MCID	Minimum clinically important difference
MD	Mean difference
MRI	Magnetic resonance imaging
NA	Not applicable
N.S.	Not significant
PI	Pelvic incidence
PT	Pelvic tilt
RR	Risk ratio
SPECT	Single-photon emission computed tomography
SRS	Scoliosis Research Society
SS	Sacral slope
TLIF	Transforaminal lumbar interbody fusion
VIBE	Volumetric interpolated breath-hold examination

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Virkki E, Holstila M, Mattila K, Pajulo O, Helenius I. Radiographic outcomes of immobilization using Boston brace for pediatric spondylolysis. *Scand J Surg*, 2020 Jan 1:1457496919896998.

II Virkki E, Oksanen H, Diarbakerli E, Helenius L, Pape B, Pajulo O, Gerdhem P, Helenius I. Health-related quality of life outcomes of instrumented circumferential spinal fusion for pediatric spondylolisthesis: a comparison with age and sex matched healthy controls. *Spine (Phila Pa 1976)* 2020 Dec 1;45(23):E1572-E1579.

III Virkki E, Holstila M, Kolari T, Lastikka M, Mattila K, Malmi S, Pajulo O, Helenius I. Elastic Lumbar Support versus Rigid Thoracolumbar Orthosis for Acute Pediatric Spondylolysis. A Prospective Follow-Up Study (Manuscript)

1 Introduction

The terms spondylolysis and spondylolisthesis are derived from Greek, where *spondylo* means spine, *lysis* means to divide, and *olisthesis* refers to dislocation or slipping. Therefore, the words are very descriptive, as *spondylolysis* is a fracture in the pars interarticularis of the vertebra and *spondylolisthesis* is a forward slippage of the vertebral body compared to the vertebral body caudally of it.

Spondylolysis is one of the most common causes of low back pain in the adolescent population and the most common cause of low back pain in young athletes, of whose pain it explains up to 47% (Micheli et al. 1995). In these patients, it is almost exclusively an overuse injury. If spondylolysis is bilateral and does not achieve bony union over time, it may lead to spondylolisthesis. Only a small group of patients with unhealed bilateral spondylolysis develop spondylolisthesis, but this is particularly probable if a child has a growth spurt ahead of him. The majority of the patients who develop spondylolisthesis develop only small slips, have few symptoms, and can live a normal life. Yet a small percentage of patients have ongoing symptoms of the olisthesis or develop a greater slip, and in these patients, operative treatment comes into consideration.

An important factor in the prevention of spondylolisthesis would be the best possible treatment for pediatric spondylolysis. If the patient achieves bony union of the pars interarticularis fracture, isthmic spondylolisthesis cannot develop. Previous studies have demonstrated good results in treatment of spondylolysis with various kinds of spinal braces combined with restriction of sports. However, it has not been determined whether a brace treatment increases the likelihood of achieving bony union of the spondylolysis or whether the result would be similar with only restriction of sports. For an adolescent, a spinal brace can be a mental burden, and it is also a significant healthcare expense.

The main focus of this study was to examine the effectiveness of a custom-made, rigid thoracolumbosacral brace for treatment of pediatric spondylolysis. We aimed to evaluate the bony union rates of spondylolysis with a brace treatment and also to compare them with the bony union rates of spondylolysis treated with an elastic lumbar support. Lastly, we wanted to assess the health-related quality of life (HRQoL) of these patients.

Even though the percentage of adolescent patients with spondylolisthesis that require operative treatment is small, these patients generally have a relatively long history with back pain, and their HRQoL is compromised. In this study, it was our interest to investigate the HRQoL of operatively treated spondylolisthesis patients before and after the surgery, and to establish whether they achieve a similar HRQoL as age and gender matched controls.

2 Review of the Literature

2.1 Definition of spondylolysis and spondylolisthesis

Spondylolysis is a fracture in the pars interarticularis of the vertebra (Figure 1). It is almost exclusively seen in the lumbar spine, and most of the cases are found in the fifth lumbar vertebra (L5) (Fredrickson et al 1984). Spondylolysis is presumed to be almost exclusively a stress fracture by nature (Weir et al. 1989). A single high-energy trauma is another rare cause of spondylolysis. Spondylolysis may present unilaterally or bilaterally. When it is bilateral, it may lead to spondylolisthesis, which refers to an anterior slippage of the vertebra compared to the vertebra caudally of it. In children, spondylolisthesis may also be seen secondary to an anatomical abnormality of the lumbosacral articulation (i.e. dysplastic spondylolisthesis).

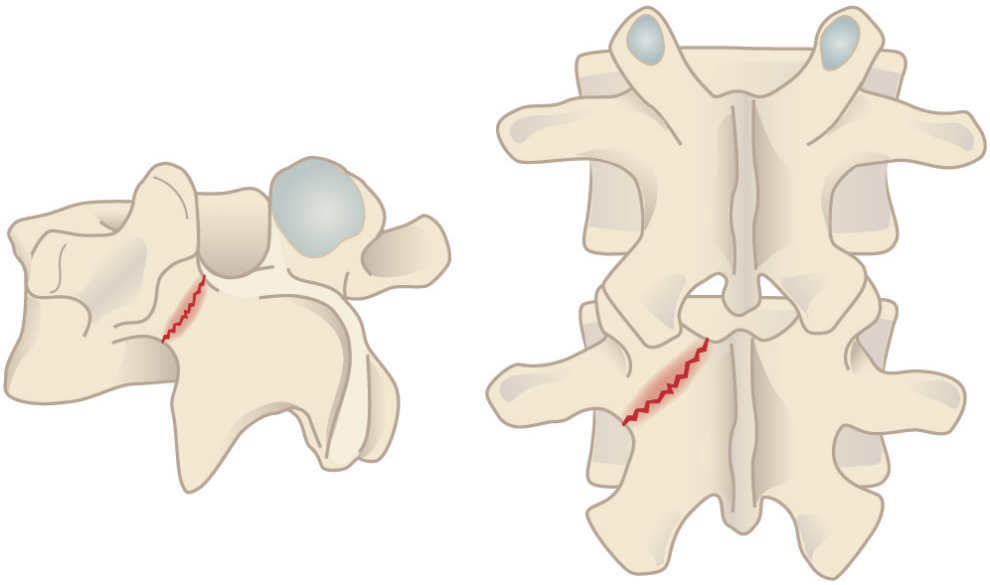

Figure 1. Anatomy of spondylolysis.

2.2 Etiology and risk factors

2.2.1 Etiology and risk factors of spondylolysis

Etiology of spondylolysis is multifactorial and acquired.

Spondylolysis is absent in newborns, and therefore its etiology is deemed not developmental but acquired (Fredrickson et al. 1984). Symptomatic spondylolysis is most often seen in adolescent athletes, which supports the acquired mechanical etiology and the nature of the defect as a stress fracture. Young athletes in sports with repetitive hyperextension and rotation, creating pressure to the pars interarticularis of the vertebra in a growing lumbar spine, are at the highest risk of developing spondylolysis. Such sports include gymnastics, baseball, soccer, pole vault, and ice hockey. Adolescents who do only one sport are at a higher risk of developing spondylolysis than multisport athletes (Selhorst et al. 2019).

A stress reaction of the pars interarticularis of the vertebra without a fracture line may lead to spondylolysis (Weir et al. 1989). This strengthens the theory of the spondylolysis being a stress fracture.

There is a genetic predisposition to spondylolysis: it has been noted that there is a higher prevalence of spondylolysis in the first-degree relatives of spondylolysis patients (Fredrickson et al. 1984, Haukipuro et al. 1978, Wynne-Davies et al. 1979, Albanese et al. 1982). These studies also report a high prevalence of spina bifida occulta among spondylolysis patients. It is known that spondylolysis is much more common in certain populations. For example, Eskimos have a higher prevalence of spondylolysis, which strengthens the evidence of genetic involvement in the etiology of spondylolysis (Tower et al. 1990). In 2015, Cai et al. reported a novel heterozygous mutation in the sulfate transporter gene SLC26A2, which they discovered to be responsible for the autosomal dominantly inherited form of dysplastic spondylolysis.

When measured, the majority of pediatric spondylolysis patients have low levels of vitamin D as their bone density remains normal. Studies conducted on this are, however, sparse and small-scale. Furthermore, in these studies, the patient volumes are small, and the straight association between vitamin D and spondylolysis remains unclear (McClellan et al. 2012, Amoli et al. 2019).

Spondylolysis may also arise as a fracture from a single high energy trauma. These cases are an exception, and the clear majority of the spondylolysis patients do not have a history of trauma (Horn et al. 2018).

2.2.2 Etiology and risk factors of spondylolisthesis

Spondylolisthesis can develop because of two underlying reasons in children: one is a bilateral spondylolysis (isthmic spondylolisthesis), and the other is a dysplasia of the facet joints of the L5 vertebra (for example spina bifida occulta, dysplastic spondylolisthesis) that allows the forward slippage of the vertebra.

The reason why only part of the people who have either a bilateral spondylolysis or a dysplastic vertebra develops spondylolisthesis remains unclear. It is known that the younger the child is (and the more growth potential remains), the more likely it is that olisthesis develops.

2.3 Prevalence and epidemiology

Low back pain is common during adolescence. Salminen et al. (1992) conducted a prevalence study of 1503 14-year-old Finnish schoolchildren and observed that 17.6% of them reported low back pain with limitation to activity in the past year. They did not examine causes of pain, but spondylolysis is one of the most common causes of low back pain in adolescents.

Spondylolysis is found in 4.4% of six-year-old children and in 6% of adults (Fredrickson et al. 1984). Only a small group of them are symptomatic. The incidence of spondylolysis has increased over time (Horn et al. 2018). Spondylolysis is twice as common in boys as in girls. Although the majority of people with spondylolysis are asymptomatic, it is the most common cause of pain in young athletes complaining low back pain, explaining up to 40-47% of the cases (Micheli et al. 1995, Nitta et al. 2016). In these studies, patients with an acute onset of symptoms were examined in hospital circumstances. Spondylolysis is overrepresented in certain athletic groups. As discussed earlier in the section concerning etiology of spondylolysis and spondylolisthesis, there is a geographical difference in the occurrence of spondylolysis and spondylolisthesis, as the Eskimos have a significantly higher prevalence of the diseases compared to other ethnic groups.

In the Finnish adult population aged 45-64, isthmic spondylolisthesis was found in 7.7% of men and 4.6% of women (Virta et al. 1992).

2.4 Natural history of spondylolysis and spondylolisthesis

The natural history of spondylolysis is not fully understood, as there is an extremely limited number of studies concerning this subject. Spondylolysis is discovered relatively often by coincidence when imaging studies of the lumbar spine area are ordered for other reasons. In these patients, spondylolysis is usually asymptomatic

at the time of the diagnosis and remains this way in most patients over time, even though no bony healing is detected (Fredrickson et al. 1984).

If the patient has bilateral spondylolysis, it is possible to develop spondylolisthesis with continued growth. It is difficult to predict whether this will happen for an individual patient, and it remains unclear why some patients develop spondylolisthesis over time while the rest do not. The slip is most likely to progress during the growth spurt, and females tend to develop greater slips compared to males (Seitsalo et al. 1988). A dysplastic form of olisthesis is also a risk factor for slip progression and developing severe slips (Seitsalo et al. 1991). Seitsalo et al. (1991) determined that if the slip was more than 20% at the first radiograph, the tendency of slip progression was greater. In the only population-based study of the natural history of spondylolysis and spondylolisthesis (Fredrickson et al. 1984), 45% of patients who had spondylolysis at the age of 6 did not develop spondylolisthesis until adulthood. Nevertheless, 70% of these patients had unilateral defects, which is known to not progress to spondylolisthesis. Of the 55% of patients who developed slip progression between the age of 6 and adulthood, the mean increase in the slip was 16% in males and 14% in females. All patients were asymptomatic. No further slip progression occurred after the age of 18. Beutler et al. (2003) prospectively studied the same population as Fredrickson et al. (1984) earlier and had a 45-year follow-up time. They noted that the clinical course of spondylolysis patients is similar to the general population, that no patient studied reached a slip over 40%, and that slip progression was not connected to low back pain.

Frennered et al. (1991) studied the natural history of symptomatic spondylolysis and spondylolisthesis in children and adolescents, following 47 patients with spondylolysis or low-grade isthmic spondylolisthesis for a mean of 7 years after diagnosis. Only two patients (4%) had a progression of the slip, and no prognostic factors for slip progression were established. In adulthood, slip progression is rare. Danielson et al. (1991) followed spondylolysis or spondylolisthesis patients under 30 years of age, and only 3% had slip progression over a mean of 3.8 year follow-up time.

2.5 Pathophysiology and biomechanics of spondylolysis and spondylolisthesis

2.5.1 Pathophysiology

Spondylolysis is considered as a stress fracture by nature based on clinical observations. It is a continuum from a stress reaction to a stress fracture and then to a bony union or a chronic nonunion. The pathophysiological mechanism is a micro-traumatic bone injury that happens especially in repeating lumbar extension

combined with axial rotation. If the L4/L5 facet joints are in a more coronal orientation, this increases the load in the rotation movement for the L5 pars interarticularis and predisposes the individual for the development of L5 spondylolysis (Ishitani 2020, Don et Robertson. 2008). This is presumed to be the reason why certain athletes are overrepresented in this patient population. Genetics may also predispose some adolescents to this injury, as the pars interarticularis is regarded as congenitally weak or dysplastic. Unilateral spondylolysis increases stress to the contralateral side of the vertebra and therefore increases the risk of stress-induced changes in the contralateral side (Sairyo et al. 2005). Spondylolysis patients are noted to have the axis of rotation of the lumbar spine deviated cranially (Sakamaki et al. 2002), and this may affect the adjacent structures of the lumbar spine and contribute to consequent spine problems.

Once there is a bilateral spondylolysis that does not heal, the vertebral body is no longer connected with the facet joints, and forward slippage of the vertebral body is possible. Spondylolisthesis patients have increased pelvic incidence (PI) (Vialle et al. 2007, Labelle et al. 2004, Roussouly et al. 2006), which could be a predisposing factor for some individuals to develop spondylolisthesis. As they have high PI, they also have high sacral slope (SS) and/or high pelvic tilt (PT), leading to increased lumbar lordosis. An emphasized lumbar lordosis leads to extra stress to the pars interarticularis of the fifth lumbar vertebra, allowing the vertebra to slip forward. Olisthesis occurs most likely during the growth spurt, but the exact pathophysiology behind this remains unclear. It is presumed that in a rapidly growing individual, the growth plates are the weakest area of the vertebra, enabling the forward slippage to develop. The pathomechanism of high-grade spondylolisthesis represents that of slipped capital femoral epiphysiolysis (Pritchett et al. 1988). In both conditions, the underlying growth plate cannot resist the sharing forces resulting in slippage.

2.5.2 Spinopelvic balance

In high-grade spondylolisthesis, the question about a balanced pelvis may arise. There are some definitions that need to be understood to evaluate whether a pelvis is balanced or unbalanced. These factors are measured from a standing lateral spine radiograph (Figure 2).

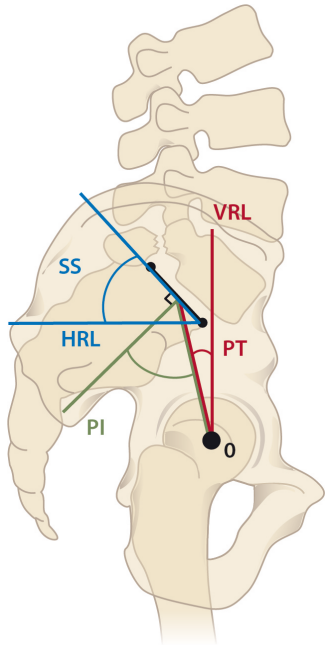

Figure 2. Pelvic measurements (Based on O'Brien et al. Radiographic measurement manual. Memphis, TN. Medtronic Sofamor Danek, 2004.).

Pelvic incidence (PI) is an angle formed between a perpendicular line drawn into the middle of the sacral endplate and a line drawn from the axis of the femoral head to the middle of the sacral endplate. PI is constant in each healthy individual after adolescence.

Sacral slope (SS) is an angle formed between a line drawn parallel to sacral end plate and a horizontal line.

Pelvic tilt (PT) is an angle formed between a line drawn from the axis of the femoral head to the middle of the sacral endplate and a vertical line drawn from the axis of the femoral head.

PI is the sum of SS and PT (PI = SS+PT).

In high-grade spondylolisthesis patients, the PI is increased (Vialle et al. 2007, Labelle et al. 2004, Roussouly et al. 2006). If the pelvis remains balanced, the SS is high, while the PT is low and lumbar lordosis is emphasized. In an unbalanced pelvis, the pelvis is retroverted with a high PT and a low SS. It has been suggested that especially high-grade spondylolisthesis patients with an unbalanced pelvis would benefit from the reduction of the olisthesis and restoring the spinopelvic balance (Hresko et al. 2007, Alzakri et al. 2019).

2.6 Diagnosis

2.6.1 Clinical presentation

A great deal of patients with either spondylolysis or spondylolisthesis are asymptomatic, and spondylolysis or spondylolisthesis is discovered by accident during imaging studies of the lumbar spine area for other reasons. But, as mentioned earlier, in an adolescent who is active in sports, spondylolysis is the most common cause of low back pain (Micheli et al. 1995).

If spondylolysis is symptomatic, the most common symptom is low back pain that worsens from exercise and extension of the spine. Pain may extend into posterior thighs (McCleary et Congeni. 2007). In the beginning, symptoms may be mitigated during rest, but as time passes, low back pain becomes more constant. Kujala et al. (1999) noted in their study that in adolescent athletes with low back pain due to acute spondylolysis or a stress reaction in the pars interarticularis, pain was particularly strong when putting weight on the lower limb of the affected side and bending backward to the same side. Sundell et al. (2013) compared various clinical tests regarding low back pain to spondylolysis found in the MRI and determined that none of the tests distinguished spondylolysis from other causes of low back pain.

Spondylolisthesis patients have similar symptoms as spondylolysis patients. In addition, these patients may develop radicular symptoms when the slipping vertebra stretches or compresses the nerve roots. Nerve root impingement may lead to tight hamstring syndrome (Kayser et al. 2006). In severe spondylolisthesis, a drop can be palpated in the lumbar spine. Female spondylolisthesis patients tend to have bigger slips and more symptoms.

2.6.2 Imaging studies

The basic imaging study of a child or an adolescent with low back pain is a standing posteroanterior and lateral radiograph of the lumbar spine. Normal radiographs do not exclude presence of spondylolysis, as they are quite insensitive (Congeni et al. 1997, Kobayashi et al. 2013). Sensitivity of two-view plain radiographs ranges from 0.59 to 0.78, and four-view radiographs do not add sensitivity when compared to two-view radiographs (Beck et al. 2013, Miller et al. 2013). Specificity of radiographs for spondylolysis is 0.96 (Beck et al. 2013). Lateral radiograph of the lumbar spine is the only imaging study taken in an upright position and is therefore the best imaging modality when evaluating spondylolisthesis and the percentage of the slip and slip progression in spondylolisthesis patients.

In Finland and in many other wealthy western countries, quite often even the first line imaging study or a study taken after plain radiographs of a child or an adolescent

complaining low back pain is a magnetic resonance imaging (MRI). This can be taken instead of plain radiographs because it does not exposure patients to ionizing radiation and the information is multiplied compared to lumbar spine radiographs. Price and availability are still the biggest limitations for the use of MRI as a screening tool in children with low back pain.

MRI is a good tool in detecting edema of the pars interarticularis. However, it is criticized for not detecting the fracture line as sensitively as other imaging modalities and therefore not differentiating stress reactions and spondylolysis accurately (Rush et al. 2015, Campbell et al. 2005, Ganiyusufoglu et al. 2010). Therefore, a targeted computed tomography (CT) has been recommended as a specifying imaging study if there is unclarity about the presence of a fracture line (Campbell et al. 2005). On the other hand, MRI recognizes early lesions (stress reactions) which could lead to a fracture if not treated, and these lesions are often not observed in a computed tomography. The sensitivity and specificity of MRI depend greatly on the slices taken (Ang et al. 2016, Saifuddin et al. 1997). With thin-slice 3D volumetric interpolated breath-hold examination (VIBE), MRI is even as sensitive and specified as CT. However, this is not a standard method for MRI of the lumbar spine.

CT has been considered the golden standard in diagnostics of spondylolysis. It is not accurate in detecting stress reactions without a fracture line, or in determining whether spondylolysis is active or a chronic pseudoarthrosis. It is still more accurate than radiographs (Fadell et al. 2015). CT is regarded as the best imaging modality for evaluating the fracture anatomy and the bony healing of the fracture (Dunn et al. 2008). The problem with the use of CT as the first line investigation in children is radiation. This can be minimized by using limited or focused CT and/or low threshold CT. CT is used as a reference imaging modality when other imaging modalities are evaluated for detecting spondylolysis, and therefore its sensitivity and specificity can be assumed to be 1.0. Comparison of imaging modalities in Table 1.

Bone scintigraphy (bone scan) and single-photon emission computed tomography (SPECT) bone scanning are other imaging modalities used for diagnosis of spondylolysis. Sanpera et al. (2006) investigated bone scan as a screening tool for examining low back pain in children. They used the SPECT technique to increase sensitivity. In their study, 30% of spondylolysis cases appeared negative in a SPECT bone scan (sensitivity 0.69). However, they assume that the unobserved lesions were inactive in the scan because they were pseudoarthrosis and therefore not the reason for low back pain in the patient. This is a problem with bone scan and SPECT, where the technique is based on intake of radioisotope to abnormally active areas. It does not recognize chronic lesions or other reasons for low back pain that are not in the spine (tumors, infection etc.). SPECT does also have a high radiation dose, which is not optimal for children.

Table 1. A comparison of different imaging modalities for detecting spondylolysis.

MODALITY	SENSITIVITY	SPECIFICITY	NOTES
2-view radiography	0.59–0.78	0.96	Only study that can be taken in upright position
MRI	0.57–0.977	0.81–0.996	Detects stress reaction, but evaluation between stress reaction and incomplete fracture is difficult especially without thin-slices
CT	1.0	1.0	Does not recognize stress reactions without a fracture line
BONE SCAN / SPECT	0.69	0.91	Does not recognize inactive lesions High radiation dose

2.7 Classifications

2.7.1 Classification of spondylolysis

Spondylolysis classification systems are based on imaging studies (MRI / CT) and categorize spondylolysis based on the acuteness of the defect. This can predict the healing potential of the lesion.

Hollenberg et al. presented an MRI-based classification in 2002. In this classification, lumbar pars interarticularis is evaluated from sagittal MR images, abnormal marrow signal is evaluated from T2-weighted fat-presaturated images, and an abnormal morphology is evaluated from T1-weighed images. Based on these evaluations, spondylolysis is divided to grades 0–4 as follows:

- Grade 0: normal
- Grade 1: stress reaction without fracture line
- Grade 2: marrow signal abnormalities with irregularity of the pars interarticularis (incomplete fracture)
- Grade 3: abnormal marrow signal with a visible complete fracture
- Grade 4: complete fracture without abnormal marrow signal (pseudoarthrosis)

In 2004, Fujii et al. presented a CT-based classification for spondylolysis. It is derived from a classification used for plain radiographs. In this classification, spondylolysis is divided to three stages accordingly:

- early lesion
- progressive lesion
- terminal lesion

In an early defect, there is a fissure in the pars interarticularis; whereas in the progressive lesion, the fracture is narrow, but its edge is round. Terminal stage lesion is a defect where the fracture is wide and there is sclerosis. This can be understood as pseudoarthrosis.

2.7.2 Classification of spondylolisthesis

There are two main classifications which are used to classify spondylolisthesis: one based on the etiology of the slippage and the other based on the percentage of the slippage.

The Wiltse-Newman classification was presented by Wiltse et al. (1976) and is based on the underlying pathology causing spondylolisthesis. It divides spondylolisthesis to five types of which only types one, two, and rarely four are present in children (Table 2).

Table 2. Wiltse-Newman Classification for spondylolisthesis.

TYPE	SUBTYPE
1. Dysplastic	
2. Isthmic	
	2A. Lytic secondary to stress fracture
	2B. Elongated pars results from multiple healed microtraumas
	2C. Acute fracture due to a single event
3. Degenerative	
4. Traumatic	
5. Pathologic	

In the Meyerding classification (Meyerding 1932), spondylolisthesis is divided by the degree of slippage. This classification divides spondylolisthesis into five grades based on the percentage of the slip as seen in Figure 3. The grade of the

spondylolisthesis is evaluated from a standing lateral radiograph of the lumbar spine. Grades I and II (slip 1-50%) are considered as low-grade, and grades III and IV (slip 51-99%) are considered as high-grade. The fifth grade is spondyloptosis, where the slip is 100%. This classification is often crucial when planning the treatment of the spondylolisthesis, as high-grade spondylolisthesis is usually treated operatively.

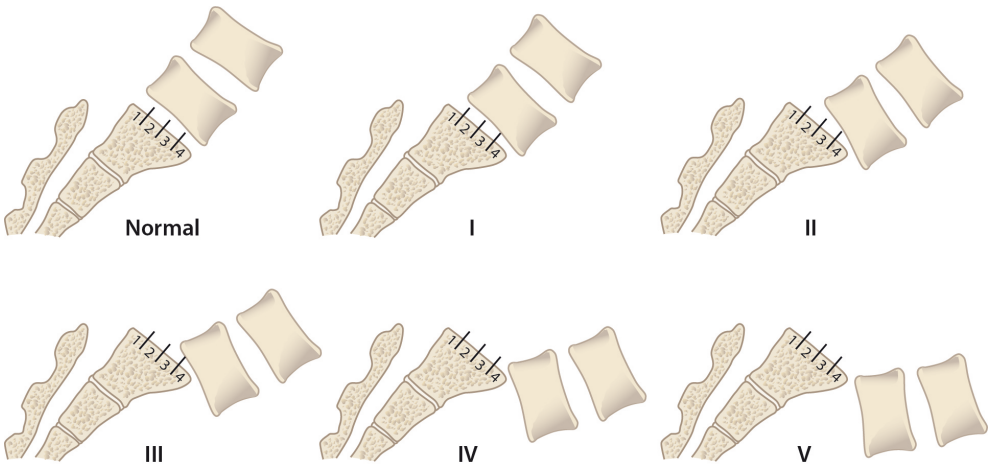

Figure 3. Meyerding classification for spondylolisthesis (Based on Meyerding 1932).

2.8 Treatment of spondylolysis

2.8.1 Conservative treatment of spondylolysis

The first-line treatment of pediatric spondylolysis is always conservative. An exception is a spondylolysis that is found by coincidence, which does not require any treatment. Conservative treatment can consist of restriction of sports, physical therapy, and an immobilization of the trunk with a brace or a corset. The goal of the treatment is to relieve pain and to achieve bony union of the pars interarticularis fracture.

Good results of achieving bony healing with a brace have been reported (Sairyo et al. 2009, Fujii et al. 2004, Sairyo et al. 2012, Sys et al. 2001, Sakai et al. 2017) (Table 3). However, there is a lack of studies comparing different kind of brace treatments or comparing brace treatment to conservative treatment with only restriction of sports or natural history of spondylolysis (Crawford et al. 2015). There is not a unanimous consensus whether a brace adds value to the treatment, and some instances use the brace, while others do not.

Multiple different types of braces have been used for treatment of spondylolysis. Micheli et al. (1980) concluded that a Boston brace is favorable in treatment of

pediatric spondylolysis due to its antilordotic straightening of the lumbar spine. A biomechanical analysis to clarify the best type of orthosis for spondylolysis patients was performed by Fujimoto et al. (2020). They conducted lumbar spine range of motion measurements for ten healthy volunteers and discovered that a custom-made lumbo-sacral orthosis had the highest restriction in all directions when compared to a soft lumbo-sacral orthosis, a custom-molded back cast-panel, a Damen type elasticity corset, and an off-the-shelf soft lumbo-sacral orthosis.

A modified Boston brace was introduced for treatment of spondylolysis as early as the 1980 by Micheli et al. They investigated the use of a Boston brace for multiple back injuries in athletes and observed good results in the treatment of spondylolysis: all 12 spondylolysis patients could fully participate in sports and had no or only some residual pain.

Sairyo et al. (2009) reported a study of 23 children with spondylolysis treated with a Damen soft thoracolumbosacral brace. They classified lesions as early, progressive, or terminal based on their appearance in the CT taken before treatment. Of these lesions, 87%, 32%, and 0% healed with a three-month brace treatment, respectively.

Fujii et al. (2004) retrospectively evaluated 134 adolescents with spondylolysis treated with a Damen corset for three months. They also classified spondylolysis as early, progressive or terminal based on their appearance radiographs and CT, and established that 62% of the early, 8.7% of the progressive, and 0% of the terminal defects had bony union after treatment. They noticed that in addition to the stage of the spondylolysis, union was affected by the spinal level of the defect, the site of the defect in the pars, the presence or development of spondylolisthesis, the condition of the contralateral pars, the degree of lumbar lordosis, and the degree of lumbar inclination.

Tatsumura et al. (2021) examined factors that were associated with failure of bony union of adolescent spondylolysis and discovered that lesion level (L5), contralateral pseudoarthrosis, and stage of spondylolysis (progressive) were such factors.

A hard thoracolumbosacral orthosis was used to immobilize the trunk in the study conducted by Sairyo et al. (2012). They had 37 patients under 18 years of age, who were CT scanned at 3 months and 6 months. They noted that healing time for early lesions was 3.2 months, and for progressive lesions 5.4-5.7 months, depending on whether those had high or low signal intensity in the MRI. The union rates were 94% for early defects, 64% for progressive with high signal intensity, 27% for progressive with low signal intensity, and 0% for terminal defects.

Sys et al. (2001) treated 28 young athletes with a hard Boston overlap Brace for a mean of 15.9 weeks. They had young adults included in the study group, as the age range of patients was 12-27 years, mean age being 17.2 years. They divided patients

to three groups: unilateral, bilateral, and pseudo-bilateral (tracer uptake in both sides in scintigraphy but uptake is clearly asymmetrical). They controlled the bony union of the fracture for a mean of 13.2 months after beginning the treatment. It was noted that all (100%) unilateral fractures had healed, five out of nine (56%) of the bilateral fractures had healed, and none of the pseudo-bilateral lesions had healed. Of the patients, 89.3% returned to the same level of competitive activity as before spondylolysis was diagnosed. Sys et al. (2001) also asked the patients to rate the outcome, and 82.2% rated the outcome as excellent, 10.7% as good, and 7.1% as fair. Ratings did not follow the rates of bony union in patients.

Sakai et al. (2017) reviewed 63 pediatric spondylolysis patients treated with a thoraco-lumbo-sacral type trunk brace (Sairyo-model hard corset). They took MRIs monthly, and when a high signal change was observed, a CT was performed to assess bony healing. Terminal stage defects were seen as pseudoarthrosis and if only this stage defects were present they were excluded from the conservative treatment protocol, as earlier studies had shown no healing potential in them. They divided lesions to very early (stress reaction), early, progressive, and terminal. The healing rates were 100%, 93.8%, 80%, and 0%, respectively. Since they took the MRI monthly, the treatment time was dependent on this and not set prior. The treatment times were 2.5 months in the very early group, 2.6 months in the early group, and 3.6 months in the progressive group. The recurrence rate of symptoms was high, 26.1%, and the majority of recurrence of symptoms occurred in the stress reaction group.

Yamazaki et al. (2018) had a retrospective study of 127 adolescents diagnosed with spondylolysis and treated with different kinds of orthosis for 3 months: patients who had very early or early lesion in CT were treated with a Damen corset, and patients with progressive or terminal defect of contralateral pars defect were treated with a hard brace. All patients returned to their previous activity level. The overall union rate was 70%, and 84.2% of the very early, 88.4% of the early, and 37.1% of the progressive lesions healed. They found that high defect stage, contralateral defects, and poor flexibility were negative predictive factors for achieving bony union of the pars interarticularis fracture.

Congeni et al. (1997) studied 40 patients under 20 years of age with spondylolysis initially treated with a nonrigid lumbar brace for 8-12 weeks; and Miller et al. (2004) did a telephone survey for these patients 7 to 11 years after the diagnosis. Two of the 40 subjects were placed in a rigid lumbar brace after four weeks of treatment with a nonrigid brace. A CT was taken at the end of the brace treatment, and in it, 18 (45%) patients did not have evidence of bony healing, 16 (40%) had potential for bony union, and 6 (15%) patients showed a bony union. On the telephone survey conducted 7 to 11 years after the diagnosis, Miller et al. (2004) determined that 91% had good or excellent low back outcome scores, and none of

the patients had required spinal fusion. Two patients (6%) reported that their back disease had influenced their career choices.

Leonidou et al. (2015) reported a series of 44 patients with spondylolysis or low-grade spondylolisthesis treated conservatively with a thoracolumbosacral orthotic brace for 6 months. Of these patients, 19 had spondylolysis without olisthesis, and 11/19 (58%) achieved bony healing. None of the spondylolysis patients developed spondylolisthesis.

Morita et al. (1995) reported the radiological outcome of 185 patients diagnosed with spondylolysis aged under 18 years and treated with a restriction of sports and a conventional lumbar corset for three to six months. 87 (73.0%) of 119 early defects had bony union after treatment, whereas 42 (38.5%) of 109 progressive lesions had union at the end of the treatment. None of the terminal defects achieved bony healing.

There is a meta-analysis of the radiological and clinical outcome of treatment of spondylolysis and grade I spondylolisthesis in children and young adults performed by Klein et al. (2009). This meta-analysis indicated that the clinical outcome is successful in 83.9% of patients, and bracing does not appear to influence it. Many of the studies in this meta-analysis were relatively old and radiographic outcome was evaluated from the plain radiographs, which makes this information outdated.

d'Hemecourt et al. (2002) treated 73 adolescents diagnosed with spondylolysis with an antilordotic lumbosacral orthosis for 6 months and reported a favorable clinical outcome in 80% of patients.

Kurd et al. (2007) examined the functional outcome of 436 symptomatic isthmic spondylolysis patients aged between 9.1 and 17.9, who were treated with a custom fit thoracolumbar orthosis and activity cessation for 3 months. They did not report the bony union rates. The functional outcome was assessed with modified Odom's criteria. Ninety-five per cent of the patients achieved excellent results which indicate relief of all pretreatment symptoms.

Sousa et al. (2017) contacted 61 adolescents with spondylolysis at a mean of 8 years after the diagnosis. Eighty-nine per cent of the patients had initially been treated with a brace. Seventy-four per cent of the patients did not show definitive healing of the pars fracture on their latest available follow-up imaging. When patients were interviewed by phone at a mean of 8 years after treatment, 35 (58.3%) patients reported no pain, whereas 25 (41.6%) reported persistent pain. Over half of the patients reporting pain rated it as 4 or higher on a scale from 0 to 10. There was no correlation with radiographic healing and the pain ratings. Of the 61 patients, 50 (82%) returned to sports, eight (13%) did not, and five (8%) returned to most but not all of their sports. Neither in this area was any correlation seen between returning to sports and achieving bony union of the defect at initial treatment.

Boyd et al. (2019) studied the functional outcomes of adolescent patients with spondylolysis or grade I spondylolisthesis treated with a non-bracing conservative

management. Ten patients had spondylolysis and 13 had grade I spondylolisthesis. They contacted the patients at a mean of 6.7 years after the diagnosis via telephone and examined their disability scores. Of spondylolysis patients, 80% had disability score of zero, which refers to no pain or limitation in any area.

In young athletes, an important factor in evaluating recovering from pars interarticularis stress fracture is return to sports. In a meta-analysis performed by Grazina et al. (2019), it was noted that 92% of the conservatively treated spondylolysis patients returned to sports at any level, and 89% returned to their pre-injury level of sports at an average of 4.6 months after diagnosis. In this meta-analysis, adult studies were also included.

The use of low-intensity pulsed ultrasound (LIPUS) was investigated in a study by Tsukada et al. (2019). They discovered that patients who received LIPUS returned to sports activities in 61 days, while patients who did not receive LIPUS returned to sports activities in 167 days. They did not report bony healing rates.

Table 3. Studies of brace treatment for spondylolysis with treatment times and bony union rates.

BRACE TYPE	TREATMENT TIME	NUMBER OF PATIENTS	BONY UNION RATE	STUDY
Damen soft corset	3 months	23	early lesions 87%, progressive lesions 32%, terminal lesions 0%	Sairyo et al. 2009
Damen soft corset	3 months	134	early lesions 62%, progressive lesions 32%, terminal lesions 0%	Fujii et al. 2004
Hard thoracolumbosacral orthosis	3 to 6 months	37	early lesions 94%, progressive lesions with high signal intensity 64%, progressive lesions with low signal intensity 27%, terminal lesions 0%	Sairyo et al. 2012
Hard boston overlap brace	12–32 weeks, mean 15.9 weeks	26 young adults included	unilateral defects 100%, bilateral defects 56%, pseudo-bilateral defects 0%	Sys et al. 2001

BRACE TYPE	TREATMENT TIME	NUMBER OF PATIENTS	BONY UNION RATE	STUDY
Thoraco-lumbo-sacral type trunk brace (Sairyo-model hard corset).	mean 2.5 months in the very early group, mean 2.6 months in the early group, mean 3.6 months in the progressive group	63	very early lesions 100%, early lesions 93.8%, progressive lesions 80.0%	Sakai et al. 2017
Damen corset for very early / early defects a hard brace for progressive defects or if contralateral pars defect	3 months	127	very early lesions 84.2%, early lesions 88.4%, progressive lesions 37.1%	Yamazaki et al. 2018
Nonrigid brace	8 to 12 weeks	40	45% nonunion, 40% potential for bony union, 15% bony union	Congeni et al. 1997
Thoracolumbosacral orthotic brace	6 months	19	58%	Leonidou et al. 2015
A conventional lumbar corset	3 to 6 months	185	early lesions 73%, progressive lesions 38.5%, terminal lesions 0%	Morita et al. 1995

2.8.2 Surgical treatment of spondylolysis

If conservative treatment of pediatric spondylolysis fails, surgery might come into consideration. In this context, failing is not defined as not achieving bony healing of the pars fracture but as ongoing symptoms, after conservative treatment over 6 to 12 months, that affect the patient's daily life. Most of the patients are symptom-free after conservative treatment, regardless of whether they reach bony union to the pars interarticularis fracture line (Kurd et al. 2007).

There are several techniques for surgical treatment of spondylolysis. All studies concerning surgical techniques are quite small and there are very few studies comparing different surgical techniques or randomizing patients to different operative treatments. Many of the studies include low-grade spondylolisthesis patients in the study population. This is due to the rarity of the operative treatment for pediatric spondylolysis.

A direct repair of the lysis and a short fusion are widely used techniques in children and adolescents for the operative treatment of spondylolysis. Direct stabilization can be achieved with a hook screw fixation, straight screw repair of the

pars, or by wiring transverse process to spinous process. An in situ L5-S1 posterolateral fusion might be preferable if there is instability. In short fusion, the normal motion at the fused level is also lost. Some authors (Smith et al. 1999) prefer an in situ fusion for L5 spondylolysis and a direct repair for upper levels, as they hypothesize that many spondylolytic defects at L5 are the end result of a developmentally weakened and elongated pars, and therefore direct fixation is not optimal.

There is no consensus on which of the direct stabilization techniques is primary. There are few studies that favor straight screw repair. A direct screw repair, also known as Buck's procedure (Buck 1970), is mini-invasive and has good results. Snyder et al. (2014) had a series of 16 patients; in these patients, the fusion rate was 89.6%, while symptoms resolved totally or partially in 93.8% of patients. When revision surgeries are considered, the overall fusion rate was 96.6%. Spondylolysis has been observed to add stress and increase the load on adjacent segments of the spine, which might increase degeneration in these areas. Buck's repair has been noted to decrease this load to a normal level (Sairyo et al. 2006).

Shin et al. (2012) compared Buck's procedure with a universal hook system and noticed that with Buck's procedure, the union rate was significantly higher than with the universal hook system (93.3% vs 78.3%).

Schlenzka et al. (1993) compared uninstrumented segmental fusion with direct repair with a cerclage wire fixation according to Scott with a mean follow-up of 54 months. They found no significant difference between the groups in the subjective, clinical, and functional outcomes. Bony union was not clearly assessed. In 2006, Schlenzka et al. evaluated same patients after 14.8 years of follow-up. At this point, total scores for health-related quality of life (HRQoL), measured with the mean Oswestry Disability Index and Scoliosis Research Society (SRS), were better in the fusion group compared to the direct repair group. In this study, low-grade spondylolisthesis patients were also included.

2.9 Treatment of spondylolisthesis

2.9.1 Conservative treatment of spondylolisthesis

Most patients with low-grade spondylolisthesis are asymptomatic and do not require any treatment. If symptoms are present, the first-line treatment for low-grade spondylolisthesis is always conservative (Gagnet et al. 2018, Klein et al. 2009). Conservative treatment aims to relieve pain, as bony union is not usually achieved due to a gap between the fracture parts. Conservative treatment can consist of pain medication, restriction of sports, physical therapy, and bracing. (Seitsalo 1990, Wiltse et al. 1976, Lonstein 1999). Treatment time should be individual, depending

on how fast symptoms are relieved. Most patients have a favorable outcome after conservative treatment. If conservative treatment fails, which means that the patient has ongoing symptoms after six to twelve months of conservative treatment, or the slip increases to high-grade, operative treatment should be considered. As mentioned earlier, in a small percentage of patients, spondylolisthesis progresses during growth. Therefore, even asymptomatic pediatric spondylolisthesis patients should be followed throughout their growth until skeletal maturity is achieved to detect progression of the slip and worsening of the symptoms during the growth spurt.

2.9.2 Operative treatment of spondylolisthesis

Widely accepted indications for surgical treatment of spondylolisthesis are a low-grade spondylolisthesis with ongoing symptoms after six to twelve months of conservative treatment or a high-grade spondylolisthesis (Lonstein 1999). A high-grade spondylolisthesis is an indication for surgery, as the slip progression and symptoms are more common (Saraste 1987). Opposite opinions have also been presented, as Lundine et al. (2014) suggested that "watchful waiting" is safe in asymptomatic or minimally symptomatic high-grade spondylolisthesis patients but noted that 40% of them required surgery during follow-up.

The most commonly used procedure is a bilateral posterolateral fusion. In a low-grade spondylolisthesis, a single level L5-S1 fusion is sufficient, whereas in a high-grade spondylolisthesis, the fusion is extended from L4 to S1 (Agabegi et al. 2010). There is controversy in the literature whether surgical technique should include reduction of the slippage. Reduction decreases the rate of pseudoarthrosis significantly and is better in normalization of spinopelvic balance (Muschik et al. 1997, Longo et al. 2014). There appears to be no difference in developing neurologic deficits or clinical outcomes. Poussa et al. (2006) noted that the HRQoL was better in spondylolisthesis patients operated with in situ fusion when compared to patients treated with an operative technique including reduction in a long-term follow-up. Spondyloptosis (100% slip) is its own entity, as reduction or removal of the slipped vertebra is associated with a high risk of nerve root deficit (Gaines 2005). Therefore, many spine surgeons prefer a technique of in situ fusion with transsacral pedicle screws reaching the slipped L5 vertebra.

2.10 Health-related quality of life

There are various kinds of questionnaires used to measure the HRQoL of a patient. One of the most widely used questionnaires for adolescent patients with back conditions is the Scoliosis Research Society -24 (SRS-24) outcome questionnaire (Haher et al. 1999). The Scoliosis Research Society (SRS) originally developed an

outcome questionnaire to measure the HRQoL of adolescent scoliosis patients. The original questionnaire was named SRS-24. Updated versions of the questionnaire have been published subsequently, for example SRS-23 and SRS-22. Some instances adopt the updated versions of the questionnaire as they are published, while others continue to use the original version to better compare answers from different years. Changes in the questionnaire versions are small, and results from different versions are comparable. Gutman et al. (2017) validated the SRS-22fv for the use of measuring HRQoL of adolescent spondylolisthesis patients and found that it can reliably be used for this purpose.

The SRS-24 questionnaire consists of 24 questions that measure the patient's satisfaction with treatment, self-image, and symptoms. It has seven domains: pain, general self-image, general level of activity, function from back condition, postoperative self-image, postoperative function, and satisfaction with treatment. Each question is scored from 1 to 5. The higher the score, the better the outcome. The total maximum score of this questionnaire is 120, which is divided by the number of questions, leading to maximum score of 5.0. Questions 16 to 24 concern treatment and can be answered only after the treatment.

Carreon et al. (2010) defined a minimum clinically important difference (MCID) in SRS-22 for appearance, activity, and pain domains after operative treatment for adolescent idiopathic scoliosis. They defined MCID as a score of 0.98 for appearance, 0.08 for activity, and 0.20 for pain domain. Rushton et al. (2013) defined MCID in SRS-22r for untreated AIS patients and normal controls. A large number of patients is needed to define MCID, and therefore such MCID for spondylolisthesis or spondylolysis patients is difficult to define, as patient populations are small. It can be assumed that the MCIDs in spondylolysis and spondylolisthesis patients would be quite similar as in adolescent scoliosis patients.

There is very limited information on the HRQoL of adolescents with spondylolysis or spondylolisthesis. Zusman et al. (2021) compared the HRQoL of adolescent spondylolysis patients with that of age matched controls and preoperative adolescent idiopathic scoliosis patients. They noted that spondylolysis patients have statistically significantly lower SRS-22 scores in pain, function, and self-image domains compared to age matched controls and AIS patients. The difference in these domains was also greater than the MCID, when compared to the control cohort. In this study, the SRS scores of spondylolysis patients were only measured prior the possible treatment of spondylolysis. Miller et al. (2004) measured the functional outcome of forty early detected adolescent spondylolysis with a low-back outcome score. An average of nine years after treatment, 91% of the patients had an excellent functional outcome. In their study, bony healing of the spondylolysis was reported in only eleven patients, and it was unclear if achieving bony union affects the functional outcome.

There are some studies regarding the HRQoL of operatively treated spondylolisthesis patients. HRQoL improves in spondylolisthesis patients after surgery (Bourassa-Moreau et al. 2013, Tsirikos et al. 2016 and Bourassa-Moreau et al. 2019). This happens especially in the high-grade spondylolisthesis patients and if the baseline scores of the SRS have been low. Joelson et al. (2018) studied high-grade spondylolisthesis patients three decades after fusion in situ and noted that they had lower SRS-22r scores in self-image and function domains than age and gender matched controls. Helenius et al. (2008) compared the long-term HRQoL of operatively treated AIS patients and fusion in situ operated spondylolisthesis patients and observed that general self-image, postoperative self-image, and postoperative function scores are lower in the spondylolisthesis patients.

3 Aims

1. To examine the bony union rates of pediatric spondylolysis treated with a hard thoracolumbosacral brace. (I, III)
2. To clarify factors affecting the bony union of the spondylolysis. (I, III)
3. To compare bony union rates of pediatric spondylolysis treated with a rigid thoracolumbar brace or an elastic lumbar support. (III)
4. To examine the HRQoL of pediatric spondylolysis patients treated with a rigid thoracolumbar brace or an elastic lumbar support. (III)
5. To evaluate the rate of pseudoarthrosis and complications as well as the HRQoL of operatively treated adolescent spondylolisthesis patients. (II)

4 Materials and Methods

4.1 Study hypotheses and aims

In study I, the hypothesis was that a rigid thoracolumbar orthosis treatment would heal most early cases of spondylolysis, while more advanced lesions would heal less often. The primary aim of study I was to determine the bony union rate of the spondylolysis when using a rigid thoracolumbar orthosis. The secondary aim was to clarify whether the level of the lesion, unilaterality, or grade of the spondylolysis would affect the healing potential.

In study II, the hypothesis was that an instrumented reduction and spinal fusion for treatment of pediatric spondylolisthesis would improve patients' health-related quality of life. Additionally, the aim was to establish whether surgically treated spondylolisthesis patients would reach the same health-related quality of life as controls and whether there is a difference in the health-related quality of life between low-grade and high-grade spondylolysis patients. A secondary aim was to observe the complication rate and radiographic outcome of the surgery.

In study III, the primary hypothesis was that a rigid thoracolumbar orthosis would improve the bony union rate of spondylolysis when compared to an elastic lumbar support. The secondary aim was to determine the spondylolysis patients' HRQoL before and after the treatment as well as predictive factors for achieving bony union of the pars defect.

4.2 Subjects

4.2.1 Study participants

Study I was retrospective in nature. Subjects in study I were spondylolysis patients, aged under 18 years at the time of the diagnosis, who were treated with a rigid thoracolumbar orthosis in our academic medical center between the years 2010 and 2018. A total of 68 patients were included in this study.

Studies II and III were prospective. Study II examined twenty-six operatively treated spondylolisthesis patients aged 10-18 from May 2009 to November 2017. They had a pedicle screw instrumentation with intercorporeal fusion using

transforaminal lumbar interbody fusion (TLIF) cage or autologous bone graft. Nerve root decompression for nerve roots L5, S1, and cauda equinae was performed. One patient had spondyloptosis (100% slip) and had transsacral instrumentation and bone grafting in situ, while all the other patients had reduction of the vertebra performed. Patients with low-grade spondylolisthesis had pedicle screws inserted into L5 and S1, and patients with a high-grade slip underwent instrumentation from L4 to S1 with iliac or S2A1 screws.

Study II had a control group matched to spondylolisthesis patients by age and sex. Each spondylolisthesis patient was matched with two healthy controls. Controls were obtained from a Swedish population-based study, in which 272 adolescents and adults were asked to fill a modified version of the original SRS, the SRS-22r questionnaire (Diarbakerli et al. 2017).

For study III, 50 acute spondylolysis patients aged 10-17 at the time of the diagnosis were recruited prospectively between June 2016 and October 2020.

4.2.2 Inclusion and exclusion criteria

Inclusion criteria for study I included age under 18 years and a spondylolysis treated with a thoracolumbosacral orthosis. Once patients were identified, their medical history and imaging studies were re-evaluated.

In study II, inclusion criteria included a surgically treated spondylolisthesis in age between 10 and 18 years.

In study III, patients aged between 8 and 18 years with an acute spondylolysis that had bone edema in the MRI and no bony sclerosis in the CT were asked to participate in the study.

Exclusion criteria for all studies (I, II, III) included a systemic illness potentially affecting bone density or bony healing. Additionally, in study I, a high energy trauma prior the diagnosis was an exclusion criterion. In study III, spondylolisthesis on a standing lumbar spine radiograph or lack of interest were additional exclusion criteria.

4.3 Study designs

4.3.1 Study I

In study I, eligible patients were identified, and their patient history was re-evaluated. Patients' imaging studies were re-evaluated by an independent musculoskeletal radiologist. She graded spondylolysis from the MRI taken before treatment according to Hollenberg et al. (2002) and evaluated the bony union of the spondylolysis from the MRI taken at the end of the brace treatment.

4.3.2 Study II

Study II was a prospective study concerning the health-related quality of life of adolescent patients who underwent a short spinal fusion with reduction and nerve root decompression for the treatment of spondylolisthesis. Radiographic outcome and complications were also examined. Study II included 26 patients, of which 11 (42%) had a low-grade spondylolisthesis and 15 (58%) had a high-grade spondylolisthesis. All low-grade spondylolisthesis patients had undergone conservative treatment consisting of periodic brace treatment, pain medication, and restriction of sports for one year before operative treatment. Clinical and radiographic data was collected preoperatively, at 6 months, and at two years follow-up. At each visit, patients were asked to fill the SRS-24 questionnaire to evaluate their HRQoL.

In study II, there was a control group which consisted of age and gender matched healthy controls to the spondylolisthesis patients. Matching by age was done with the age of spondylolisthesis patients in their 2-year follow-up. Each spondylolisthesis patient had two matched controls. Then, the spondylolisthesis patients' HRQoL two years after surgery was compared with the control group's HRQoL.

4.3.3 Study III

Study III was started as a randomized prospective study in June 2016. Randomization was done between the brace treatments for an acute pediatric spondylolysis: a rigid thoracolumbar orthosis (Boston brace, Respecta) or an elastic, low-profile lumbar support (Porostrap, Donjoy). The first fourteen patients were randomized. The problem with randomization was that patients and their families wanted to have an influence in the brace type themselves. As over 20% (4/18) of the patients refused to participate in the study due to randomization, study design was changed in September 2018 to the patient preference arm. The last 36 patients chose the treatment option themselves. A total of 50 patients participated in this study, but two were excluded in the analyzing phase: one because spondylolysis had no bone edema in the MRI and was classified as pseudoarthrosis, and the other because of the patient's lack of interest to participate in the study before the first control. A total of 48 patients underwent analyses. Twenty-eight of them had a Boston brace and 20 had an elastic lumbar support as the treatment for spondylolysis. All patients had restriction of sports and identical physical therapy for the treatment time of four months.

In the beginning of the treatment a radiograph, an MRI and a CT of the lumbar spine were taken. From the lumbar spine radiographs, spondylolisthesis was ruled out, and from the MRI and the CT, spondylolysis was graded according to

Hollenberg et al. (2002) and Fujii et al. (2004), respectively. At the end of the treatment, a CT was taken to evaluate bony healing of the spondylolysis. All imaging studies were re-evaluated by an independent musculoskeletal radiologist.

Patients were asked to fill the SRS-24 outcome questionnaire before the treatment and at the end of the treatment. From this questionnaire, the patients' HRQoL and relief of pain were evaluated.

4.4 Statistical analyses

In study I, continuous variables were described as means (standard deviations) and ranges. Categorical variables were expressed as relative proportions (percentages). Statistical comparisons for categorical parameters were done using chi-squared tests, and unpaired t tests were used for continuous variables. Bilateral spondylolysis and no high signal intensity in MRI were used as a reference when relative risks and their 95% confidence intervals were calculated. P values under 0.05 were considered significant. The analyses were performed using Microsoft Excel for Mac software, version 16.20.

In study II, categorical variables were expressed as counts and relative proportions (percentages), whereas continuous variables were expressed as means and standard deviations. Statistical comparisons for radiographic parameters were performed with unpaired t tests, and for variation of SRS domains over time, a linear mixed model for repeated measures analysis was used. Before statistical analysis, a log-transformation was performed for the mirror transforms of the domain scores. The Kruskal-Wallis tests were used to compare the patients' SRS domain scores with controls. The p values in pairwise comparisons were adjusted for time, and p values under 0.05 were considered significant. The analyses were performed using the SAS system, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

In study III, categorical variables were described as counts and proportions (percentages), and continuous variables were described as means and standard deviations or 95% confidence intervals (CI). Fisher's exact test was used to analyze associations in categorical data, and one-way analysis of variance (ANOVA) was used to evaluate associations in continuous variables. Bony union rates of spondylolysis with different brace treatments were calculated with log-binomial models. Univariate analysis of possible predictive factors of bony union was performed; since only one significant factor was found, a multivariate model was not constructed. Risk ratio for the stage of the spondylolysis in baseline CT was not possible to calculate, as all early stage defects healed. Hence, the Cochran-Armitage trend test was performed to establish the association between the stage in baseline CT and bony union. SRS scores were analyzed with a hierarchical linear mixed model. It had repeated measures and within-factor (time), between-factor (group)

and interaction (time*group). Background characteristics were examined to determine whether they affected the mean change scores between two measurement points. Because posttreatment self-image and function domains were skewed distributed, they were analyzed with the Mann Whitney U test, and normally distributed satisfaction domain was analyzed with ANOVA. P values under 0.05 were considered significant, and all tests were performed two-sided. Analyses were performed using the SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, US).

A sample size of 22 subjects for each treatment group for study III was calculated with the use of study power of 80%, a type-I error (alpha) of 0.05. The 90% union rate with a hard brace treatment was based on the Sairyo et al (2012) study. There was lack of reliable data about the healing rate with a similar kind of soft lumbar support as was used in study III, and therefore the healing rate was assumed to be 55% based on our clinical experience. To allow for dropouts, 50 patients were included in study III.

4.5 Study permissions

For all the studies, ethical committee approval was applied. The ethical committee did not request informed consent for the patients of studies I and II. This was because study I was retrospective and in study II, spondylolisthesis patients underwent a clinically standardized treatment protocol without additional examinations. A written informed consent was acquired from the normative population of study II and all patients of study III, as well as the guardians of both populations if needed.

For all the studies, local hospital study permissions were applied and admitted.

Study III was registered to ClinicalTrials.gov (NCT03675152) before starting the study.

5 Results

5.1 Treatment of spondylolysis

5.1.1 Brace treatment

Study I was a retrospective cohort study of 68 consecutive spondylolysis patients treated with a rigid thoracolumbar orthosis, an individual custom-made Boston underarm thoracolumbar orthosis (Boston brace). All of the patients were active in sports. There were 26 (38.2%) unilateral and 42 (61.8%) bilateral defects, and therefore a total of 110 defects were seen in these 68 patients. In this study, the overall bony union rate was 44.5% (49/110 defects). As pseudoarthrosis has no healing potential, when these cases are omitted, the bony union rate raises to 58.3% (49/84 defects). The incomplete fractures healed more often than the complete fractures, 38/46 (82.6%) and 11/38 (28.9%), respectively ($p<0.001$).

In study III, treatment of spondylolysis with a Boston brace was compared to treatment with an elastic lumbar support. There was no statistically significant difference in the union rates, as twenty of twenty-eight (71.4%) of the patients treated with a Boston brace and 15/20 (75.0%) of the patients treated with an elastic lumbar support had either a unilateral defect that healed or a bilateral defect of which both sides healed (RR 1.14, 95%CI 0.44, 2.98, $p=0.785$). When defects were graded based on their appearance in the baseline CT (Fujii et al. 2004), there was no statistical difference in the healing rates of different grades of spondylolysis treated with a Boston brace or with an elastic lumbar support (Table 4).

Table 4. Bony union rates of pars interarticularis defects with different brace treatments (original publication III).

STAGE OF THE DEFECT IN THE PRETREATMENT CT (FUJII ET AL. 2004)	BOSTON BRACE (NUMBER WITH UNION / TOTAL NUMBER OF PATIENTS)	ELASTIC LUMBAR SUPPORT (NUMBER WITH UNION / TOTAL NUMBER OF PATIENTS)	P VALUE
All defects	71.4% (20/28)	75.0% (15/20)	0.785
Early	100% (13/13)	100% (5/5)	NA
Progressive	53.8% (7/13)	69.2% (9/13)	0.688
Terminal	0% (0/2)	50.0% (1/2) *	1.00

*One patient had a defect graded as terminal stage in the CT but a complete fracture in the MRI (not pseudoarthrosis) and this defect healed
NA= not applicable, values are counts and percentages

When patients treated with a Boston brace from studies I and III were combined, the overall bony union rate of pars interarticularis fractures with a rigid thoracolumbar orthosis was 51.1% (70/137) (Table 5). Patients who were in both study cohorts were excluded from study cohort III to remove duplications. In this union rate calculation, pseudoarthrosis is included – since these cases have zero healing potential, they could be omitted, and the bony union rate without pseudoarthrosis was 63.1% (70/111). Union rate for incomplete fractures was 84.8% (56/66); for complete fractures, it was 31.1% (14/45).

Table 5. Bony union rates of pediatric spondylolysis with a Boston brace.

	NUMBER WITH UNION / TOTAL (N=137)	P VALUE
All defects	70/137 (51.1 %) • excluding pseudoarthrosis 70/111 (63.1%)	
Grade of the pars defects (Hollenberg et al. 2002)		<0.001
• Incomplete fracture	56/66 (84.8%)	
• Complete fracture	14/45 (31.1%)	
• Pseudoarthrosis	0/26 (0%)	

values are counts and percentages

5.1.2 Predictive factors for the bony union of spondylolysis

In study I, unilaterality, incomplete fracture, and high signal intensity of the pars interarticularis in the MRI before treatment predicted bony union of the defect. In study I, the level of the lesion did not affect the healing rate (Table 6).

Table 6. Factors affecting bony union of the spondylolysis in study I and study III.

	THE NUMBER WITH UNION / TOTAL (%) STUDY I (N=110 DEFECTS)	P VALUE STUDY I	THE NUMBER WITH UNION / TOTAL (%) STUDY III (N=84)	P VALUE STUDY III
Grade of the pars defect in MRI (Hollenberg et al. 2002)		<0.001		<0.001
• Incomplete fracture	38/46 (82.6%)		52/56 (92.9%)	
• Complete fracture	11/38 (28.9%)		12/28 (42.9%)	
• Pseudoarthrosis	0/26 (0%)		0/0 (0%)	
Vertebral level		0.65		0.18
• Above L5	8/20 (40.0%)		13/20 (65.0%)	
• L5	41/90 (45.6%)		51/64 (79.7%)	
Laterality		0.014		0.82
• Unilateral	17/26 (65.3%)		11/14 (78.6%)	
• Bilateral	32/84 (38.1%)		53/70 (75.7%)	
High signal intensity in mri		<0.001		<0.001
• No	1/23 (4.3%)		0/2 (0.00%)	
• Yes	48/87 (55.2%)		64/82 (78.0%)	
BRACE TYPE		NA		0.73
• Boston brace	49/110 (44.5%)		38/49 (77.6%)	
• Soft brace	NA		26/35 (74.3%)	

NA= not applicable, values are counts and percentages

Similar to study I, in study III, incomplete fracture and high signal intensity of the pars interarticularis in the MRI were predictive factors for achieving bony union of the defect. In the data of study III, unilaterality could not be proved to be a predictive factor for bony union of the spondylolysis; neither could treatment with a Boston brace. In univariate analysis of the data in study III, early stage of the defect in the CT was the only factor predicting bony union, whereas patient's age, gender, laterality of the spondylolysis, level of the spondylolysis, or brace type did not affect it (Table 7).

Table 7. Predictive factors for bony union of pediatric spondylolysis in univariance analysis (original publication III).

FACTOR	RR	95% CI	P VALUE
Brace type			
• Boston Brace	Reference		
• Elastic LUMBAR SUPPORT	0.875	0.335, 2.282	0.785
Gender			
• Female	Reference		
• Male	0.659	0.261, 1.666	0.378
Laterality			
• Unilateral	Reference		
• Bilateral	1.373	0.443, 4.250	0.583
Level of spondylolysis			
• Above L5	Reference		
• L5	0.877	0.296, 2.599	0.813
Stage			
• Early	NA*		<0.001
• Progressive			
• Terminal			
Age			
• < 14.0 years	Reference		
• ≥ 14.0 years	0.833	0.330, 2.106	0.700

NA= not applicable

* Risk ratio could not be calculated because all early defects healed

5.2 Radiographic outcome and complications of an instrumented reduction and circumferential spinal fusion for the treatment of pediatric spondylolisthesis

5.2.1 Radiographic outcome

Study II included 26 consecutive adolescent patients who underwent surgical treatment for spondylolisthesis. Their characteristics are seen in Table 8. Indications for surgery were a high-grade spondylolisthesis or a low-grade spondylolisthesis with ongoing symptoms after a year of conservative treatment.

Table 8. Clinical characteristics of study II patients (Original publication II, copyright with permission).

VARIABLE	SPONDYLOLISTHESIS PATIENTS (N=26)	HEALTHY CONTROLS (N=52)
Age at 2-year FU (y)	16.7 ± 1.94	17.6 ± 3.8
Gender (male)	23% (6/26)	23% (12/52)
FU time (y)	3.3 ± 1.75	
Amount of slip		
• Low-grade (0-50%)	42% (11/26)	
• High-grade (51-100%)	58% (15/26)	
Levels fused		
• L5-s1	46% (12/26%)	
• l4-s1	54% (14/26)	
Blood loss (ml)	391 ± 185	
Operative time (h)	3.8 ± 1.3	

FU = follow-up
scores are mean values and SD or percentages and counts

Radiographic outcome was evaluated from standing radiographs of the spine (Table 9). Radiographs were taken prior the operation, at 6 months, and at 2 years after the operation. The mean (±SD) slip in the low-grade spondylolisthesis patients preoperatively was 25% (±13%), and 67% (±15%) in the high-grade spondylolisthesis patients. After operative reduction of the slip, it was 6% (±7%) and 21% (±25%), respectively. Unbalanced pelvis was seen preoperatively in eight (53%) of the high-grade spondylolisthesis patients and postoperatively in seven (47%) of the patients (N.S.)

Table 9. Radiographic parameters of low-grade and high-grade spondylolisthesis patients (Original publication II, copyright with permission).

RADIOGRAPHIC PARAMETERS	LOW-GRADE (N=11)	HIGH-GRADE (N=15)	P VALUE
Slip (%)			
• Preoperative	25% ± 13%	67% ± 15%	<0.001
• 2-yr FU	6% ± 7%	21% ± 25%	0.041
Lumbosacral angle			
• Preoperative	10° ± 8°	14° ± 11°	0.322
• 2-yr FU	10° ± 8°	10° ± 6°	0.884
Pelvic tilt			
• Preoperative	18° ± 9°	30° ± 8°	0.004
• 2-yr FU	20° ± 5°	26° ± 8°	0.044
Sacral slope			
• Preoperative	44° ± 12°	46° ± 8°	0.628
• 2-yr FU	40° ± 13°	46° ± 6°	0.164
Unbalanced pelvis			
• Preoperative	NA	57% (8/14)	
• Postoperative	NA	47% (7/15)	
Pelvic incidence	60° ± 10°	72° ± 10°	0.007

FU= follow-up, YR= year, NA= not applicable
Scores are mean values and SD

5.2.2 Complications

Complications are summarized in Table 10. Cerebrospinal fluid leak was noted and closed in the primary operation in three (12%) patients with no need for further events. Five (19%) patients reported radicular pain at least occasionally after the operation, but none developed a persistent neurologic defect. Two (8%) of these patients presented with a chronic postsurgical pain persisting two years after surgery. Need for re-operation for any reason during follow-up time was 27%. The most common cause for re-operation was mechanical discomfort from the iliac screws due to which they were removed in four (15%) patients. In one of these patients, a persistent postoperative cerebrospinal fluid leakage required a re-revision to seal the leak. Other causes for re-operation were a pseudoarthrosis in three (12%) patients, and development of spondylolisthesis at the level above the index procedure (L4-L5) in one (4%) patient.

Table 10. Complications of an instrumented reduction and circumferential spinal fusion for the treatment of pediatric spondylolisthesis.

COMPLICATION	NUMBER OF PATIENTS (N=26)
Cerebrospinal fluid leak	3 (12%)
Postoperative radicular pain	5 (19%)
Reoperation	7 (27%)
• Pseudoarthrosis	3 (12%)
• Spondylolisthesis at the level above the index level	1 (4%)
• Mechanical discomfort from the iliac screws	4 (15%)

5.3 Health-related quality of life (HRQoL)

5.3.1 HRQoL of spondylolysis patients

In study III, the spondylolysis patients' HRQoL was measured using the SRS-24 outcome questionnaire. Patients filled the questionnaire before treatment and at the end of the four-month treatment. This study demonstrated that there was no difference in the HRQoL between treatment groups at the end of the treatment (Table 11).

Table 11. Comparison of SRS-24 scores of spondylolysis patients with different brace treatments (original publication III).

SRS DOMAIN	BOSTON BRACE (BASELINE N=20, 4 MONTHS N=27)	ELASTIC LUMBAR SUPPORT (BASELINE N=20, 4 MONTHS N=19)	MEAN DIFFERENCE (95% CI)	P VALUE
Pain				
Baseline	3.42 (3.12, 3.72)	3.54 (3.26, 3.81)	0.11 (-0.28, 0.51)	0.567
4 months	4.33 (4.12, 4.55)	4.45 (4.23, 4.67)	0.15 (-0.19, 0.43)	0.452
Self-image				
baseline	4.27 (3.99, 4.55)	4.52 (4.27, 4.77)	0.21 (-0.13, 0.55)	0.215
4 months	4.25 (3.99, 4.51)	4.42 (4.04, 4.78)	0.18 (-0.24, 0.59)	0.392
Function				
baseline	3.63 (3.34, 3.92)	3.67 (3.43, 3.90)	0.02 (-0.34, 0.37)	0.915
4 months	3.85 (3.67, 4.04)	3.93 (3.68, 4.18)	0.08 (-0.21, 0.38)	0.567
Activity				
baseline	3.96 (3.48, 4.45)	3.95 (3.67, 4.22)	-0.02 (-0.55, 0.52)	0.955
4 months	4.30 (4.04, 4.56)	4.37 (3.98, 4.76)	0.06 (-0.38, 0.50)	0.785
total				
baseline	3.73 (3.48, 3.97)	3.83 (3.66, 4.00)	0.08 (-0.20, 0.37)	0.556
4 months	3.73 (3.59, 3.86)	3.85 (3.74, 3.96)	0.13 (-0.05, 0.31)	0.159
Posttreatment self-image 4 months*	3.00 (3.00, 3.00)	3.00 (3.00, 3.00)	NA	0.224
Posttreatment function 4 months*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	NA	0.844
Satisfaction 4 months	3.70 (3.43, 3.98)	3.84 (3.61, 4.07)	-0.17 (-0.57, 0.24)	0.410

Values are given as the mean and 95% CI, except * values are medians and 95% CI, NA= not applicable

When SRS-24 scores before treatment were compared with the scores after treatment, it was noted that in the pain domain, scores improved in all patients ($p<0.001$). Additionally, the activity domain improved in patients who achieved bony union of the spondylolysis. Improvement in the pain domain for all patients and in the activity domain for patients who achieved bony union exceeded the MCID defined by Carreon et al. (2010) (Table 12).

Table 12. SRS-24 scores before and after the treatment for pediatric spondylolysis in patients who achieved bony union of the pars defect and who did not (original publication III).

SRS DOMAIN	BASELINE BONY UNION GROUP (N=29)	4 MONTHS FOLLOW-UP BONY UNION GROUP (N=33)	P VALUE
Pain	3.39 (3.17, 3.61)	4.35 (4.21, 4.54)	<0.001
Self-image	4.30 (4.09, 4.51)	4.26 (4.00, 4.52)	0.497
Function	3.64 (3.46, 3.83)	3.87 (3.69, 4.04)	0.059
Activity	3.91 (3.58, 4.23)	4.39 (4.16, 4.63)	0.021
Total	3.71 (3.55, 3.87)	3.79 (3.68, 3.90)	0.471
	BASELINE NON-UNION GROUP (N=9)	**4 MONTHS FOLLOW-UP NON-UNION GROUP (N=13)**	
Pain	3.76 (3.31, 4.21)	4.40 (4.03, 4.77)	0.011
Self-image	4.70 (4.35, 5.00)	4.49 (4.14, 4.83)	0.218
Function	3.67 (3.14, 4.19)	3.92 (3.64, 4.21)	0.228
Activity	4.11 (3.61, 4.61)	4.15 (3.66, 4.65)	0.903
Total	4.01 (3.70, 4.32)	3.76 (3.59, 3.94)	0.081

Values are given as the mean and 95% CI

5.3.2 HRQoL of surgically treated spondylolisthesis patients

In study II, the HRQoL of adolescent spondylolisthesis patients was measured using the SRS-24 questionnaire. They filled the questionnaire prior the operation, at 6 months, and at two years after the operation. Their results were compared with age and gender matched controls. Matching was done with the age of the surgically treated spondylolisthesis patients in their last follow-up. Controls had filled the modified version of the SRS-24: the SRS-22r questionnaire. Its questions are either exactly the same or close to the original SRS-24 questionnaire questions, and results can be reliably compared with each other.

When comparing SRS-24 scores of spondylolisthesis patients prior the operation and at two years follow-up, it was noted that the pain and activity domains of the SRS questionnaire improved significantly from preoperative to 2-year follow-up (p=0.007, p=0.001, respectively) (Table 13). Improvement in the pain and activity domains was above the MCID defined by Carreon et al. (2010). As the SRS-24 scores of high-grade and low-grade spondylolisthesis patients were compared with each other, no statistically significant differences were found expect for the difference in the self-image domain (p=0.008, results not shown).

Table 13. The changes in SRS-24 scores of spondylolisthesis patients during follow-up time. (Original publication II, copyright with permission).

SRS DOMAIN	PREOPERATIVE (N= 22)	6 MONTHS FOLLOW-UP (N=20)	2-YEAR FOLLOW-UP (N=23)	P VALUE
Total	3.59 ± 0.61	3.82 ± 0.52	3.86 ± 0.68	0.059*
Pain	3.27 ± 0.93	4.24 ± 0.89	3.92 ±1.03	0.007*
Self-image	4.03 ± 0.63	4.11 ± 0.39	4.28 ± 0.57	0.052*
Function	3.85 ± 0.50	3.96 ± 0.52	4.10 ± 0.46	0.065*
Activity	3.53 ± 1.06	3.81 ± 1.18	4.22 ± 1.25	0.001*
Postop self-image	NA	3.18 ± 0.57	3.26 ± 0.67	0.627**
Postop function	NA	2.42 ± 1.17	3.00 ± 1.41	0.072**
Satisfaction	NA	4.02 ± 0.60	3.91 ± 0.56	0.260**

* 2-year follow-up scores compared to preoperative scores
** 2-year follow-up scores compared to 6 months follow-up scores
Scores are mean values and SD
NA= not applicable

When the SRS scores of the operatively treated spondylolisthesis patients in their 2-year follow-up were compared with controls, it was noted that the surgically treated spondylolisthesis patients had lower scores in the pain, self-image, and function domains and a lower total SRS score ($p<0.05$ for all comparisons, Table 14). The SRS scores were equal only in the activity domain. When low-grade and high-grade spondylolisthesis patients were compared separately to controls (Table 15), it was noted that high-grade spondylolisthesis patients had statistically significantly lower scores in the pain ($p=0.020$) and function ($p<0.001$) domains, whereas low-grade spondylolisthesis patients had lower scores in the pain ($p=0.002$), self-image ($p=0.027$), and function ($p<0.001$) domains.

Table 14. Comparison of SRS outcomes between surgically treated spondylolisthesis patients and age and gender matched controls (Original publication II, copyright with permission).

SRS DOMAIN	2-YEAR FOLLOW-UP (N=23)	HEALTHY CONTROLS (N= 52)	P VALUE
Total*	4.10 ± 0.76	4.73 ± 0.33	<0.001
Pain**	3.97 ± 1.02	4.76 ± 0.45	<0.001
Self-image	4.28 ± 0.57	4.57 ± 0.50	0.018
Function	4.09 ± 0.46	4.91 ± 0.19	<0.001
Activity	4.22 ± 1.25	4.66 ± 0.46	0.482
Total of 8 same questions	4.03 ± 0.89	4.67 ± 0.41	<0.001

* 2-year follow-up SRS scores excluding the questions regarding postoperative state
** the postoperative pain question is excluded
Scores are mean values and SD

Table 15. Comparison between SRS domains in the low-grade vs high-grade spondylolisthesis patients and healthy controls (Original publication II, copyright with permission).

SRS DOMAIN	LOW-GRADE 2-YEAR FOLLOW-UP (N=10)	HEALTHY CONTROLS (N= 52)	P VALUE*	HIGH-GRADE 2-YEAR FOLLOW-UP (N=13)	P VALUE**
Total ˆ	3.81 ± 0.95	4.73 ± 0.33	<0.001	4.33 ± 0.51	0.002
Painˆˆ	3.68 ± 1.25	4.76 ± 0.45	0.002	4.19 ± 0.79	0.020
Self-image	4.13 ± 0.55	4.57 ± 0.50	0.027	4.38 ± 0.59	0.457
Function	3.88 ± 0.62	4.91 ± 0.19	<0.001	4.26 ± 0.20	<0.001
Activity	3.67 ± 1.54	4.66 ± 0.46	0.150	4.64 ± 0.81	0.816
Total of 8 same question	3.74 ± 1.05	4.67 ± 0.41	0.009	4.26 ± 0.69	0.067

ˆ 2-year follow-up SRS scores excluding the questions regarding postoperative state
ˆˆ the postoperative pain question is excluded
*low-grade srs-24 2-year follow-up vs healthy controls srs-22
** high-grade srs-24 2-year follow-up vs healthy controls srs-22
Scores are mean values and SD

6 Discussion

6.1 Strengths and limitations of the data

Study I was a retrospective consecutive series. The radiographic analyses were done by an independent musculoskeletal radiologist. The size of the study (68 patients) was satisfactory. The limitations of study I include an unstandardized treatment protocol, and both MRI and CT were used to evaluate bony union of the defect. Patients were instructed to wear the brace for 23 hours per day, but there was no sensor in the brace to record the actual use of the orthosis.

In study II, the data was a prospectively collected consecutive series of 26 adolescents with an operatively treated spondylolisthesis. Indications for operation were clear. Operation was performed similarly on all patients by a single orthopedic spine surgeon. The follow-up time was a minimum of two years.

The limitations of study II include a relatively small study cohort, as operative treatment for pediatric spondylolisthesis is relatively rare. This could explain why we could not get a statistically significant difference between the HRQoL of low-grade and high-grade spondylolisthesis patients at two years after surgery. Another limitation of study II concerned the different versions of the SRS questionnaires used with spondylolisthesis patients (SRS-24) and controls (SRS-22r). We compared the questionnaire results using our best judgment.

Study III was a prospective study that started as a randomized trial; but as explained in the earlier section, study protocol was changed during data collection due to refusals to participate because of the randomization. In an ideal situation, the study would have continued as a randomized study. Similar difficulties have been seen for example in the BRAIST trial (Weinstein et al. 2013), where a randomized trial for adolescent idiopathic scoliosis was ended before the inclusion requirement was fulfilled, because patients wanted to make the decision between brace treatment and observation themselves. Other limitations of study III are a short follow-up time of only the treatment time of four months and the size of a study cohort. Follow-up time should be ideal for immobilization and to evaluate the bony union (Sakai et al. 2017), but a longer follow-up time would produce more information about the HRQoL of spondylolysis patients. A rigid thoracolumbar orthosis provides the most advanced method of spinal immobilization (Fujimoto et al. 2020) and should

therefore be the best method to immobilize the trunk for treatment of spondylolysis. Similar to study I, in study III, patients were instructed to wear the brace for 23 hours per day, but there was no sensor in the brace to record the actual use of the orthosis. In study III, the treatment protocol was standardized and identical between treatment groups except for the brace type.

All patients in studies I and III had symptoms related to spondylolysis and had actively sought professional evaluation of those symptoms. Therefore, the data is selected, and results of these studies cannot be directly generalized to all (asymptomatic) spondylolysis patients.

The SRS-24 outcome questionnaire used in studies II and III is a standardized, validated and widely used questionnaire to evaluate HRQoL.

6.2 Treatment of pediatric spondylolysis

Earlier studies have shown good treatment results with various kinds of hard orthosis for pediatric spondylolysis (Sakai et al. 2017, Sairyo et al. 2012, Yamazaki et al. 2018). In study I, results were similar, as 82.6% of the incomplete fractures and 28.9% of the complete fractures healed with a Boston brace. When patients from study III treated with a Boston brace were combined with study I patients and duplications were removed, the healing rate was 84.8% for incomplete fractures and 31.1% for complete fractures. Studies concerning the use of a soft brace for treatment of pediatric spondylolysis are mostly conducted with a Damen soft corset (Sairyo et al. 2009, Fujii et al. 2004), and the bony union rates have been good in these as well. A Damen soft corset is a relatively stiff brace compared with an elastic lumbar support (Porostrap) used in study III. Study III is to our knowledge the first prospective study comparing a rigid brace and a soft brace for treatment of an acute pediatric spondylolysis. It showed no statistically significant difference between treatment groups, and bony union rates were good in both treatment groups. Therefore, it appears that a rigid brace is overtreatment for an acute pediatric spondylolysis and that an elastic lumbar support would be equally effective.

Treatment time was three months in study I and four months in study III. As spondylolysis is a stress fracture by nature, treatment time and restriction of sports need to be longer than in regular fractures seen in children. In many earlier studies, treatment time with a brace has been three months (Sairyo et al. 2009, Fujii et al. 2004, Yamazaki et al. 2018). In a study by Sakai et al. (2017), they treated spondylolysis patients with a thoraco-lumbo-sacral-type trunk brace (Sairyo-model hard corset), took follow-up MRIs monthly after the first presentation, and confirmed bony healing with a CT scan. In their study, the average treatment time was 2.5 months for very early lesions, 2.6 months for early lesions, and 3.6 months for

progressive lesions. Therefore, the treatment time in studies I and III can be considered as sufficient.

6.3 Factors that predict bony union of pediatric spondylolysis

Several earlier studies have shown that the grade (MRI) or the stage (CT) of the spondylolysis affects the likelihood of achieving bony union of the pars interarticularis fracture (Sairyo et al. 2006, Sairyo et al. 2009, Fujii et al. 2004, Sairyo et al. 2012, Sakai et al. 2017, Yamazaki et al. 2018, Morita et al. 1995, Tatsumura et al. 2021). The results of our studies I and III are in line with this finding.

A study conducted by Sys et al. (2001) discovered that 100% of the unilateral defects healed with a Boston brace, whereas only 56% of the bilateral defects healed. Similarly, in study I, unilaterality was a predictive factor for achieving bony union of the pars interarticularis defect. The same could not be proved in study III.

Neither study I or study III could prove the vertebral level of the defect to be a predictive factor for bony union of the spondylolysis. In an earlier study by Fujii et al. (2004), vertebral level was a predictive factor for bony union: if the spondylolysis was in the L4 vertebra, it was more likely to achieve bony union than if it was in the L5 vertebra. A study by Tatsumura et al. (2021) obtained similar result. Even though results were not statistically significant in studies I and III, in both studies, healing rates were higher in the L5 vertebra than above it.

A study by Sairyo et al. (2012) observed that high signal intensity in the MRI predicts bony union of the spondylolysis. Studies I and III produced similar outcomes, as only one defect without high signal intensity in the MRI of either study group achieved bony union at the end of the brace treatment.

In a study by Tatsumura et al. (2021), in addition to level (L5) and stage (progressive) of the spondylolysis, contralateral pseudoarthrosis was associated with failure of bony union of an acute pediatric spondylolysis. In our study III, univariate analysis was done regarding the more advanced stage lesion, and therefore association with contralateral pseudoarthrosis could not be analyzed.

In study III, the brace type could not be proved to be a factor affecting bony union of the spondylolysis. There are no previous studies comparing brace types for achieving bony union of the pars interarticularis defect. More research on this topic would be needed.

6.4 HRQoL of pediatric spondylolysis patients

There is scarce documentation on the HRQoL of pediatric spondylolysis patients. Zusman et al. (2021) examined the HRQoL of adolescent spondylolysis patients and

compared it with preoperative adolescent idiopathic scoliosis patients and age matched controls. In this study, the spondylolysis patients' HRQoL was lower in the pain, function, and self-image domains of the SRS-22 questionnaire. They only characterized the SRS-22 questionnaire data in pediatric spondylolysis patients and did not measure HRQoL following treatment. Study III discovered no difference in the HRQoL of pediatric spondylolysis patients who achieved bony union compared to those who did not.

In study III, the SRS-24 score of the pain domain improved in all patients after treatment, regardless of treatment type or whether patients achieved bony union of the pars defect. In patients who achieved bony union of the defect, the activity domain improved as well. It is quite natural that regardless of the healing of the fracture, the treatment itself relieves pain, as patients are in a restriction of sports for four months. In study III, the HRQoL was similar between treatment groups at the end of the treatment.

In future studies, it would be interesting to see how the HRQoL of spondylolysis patients changes after the end of the treatment, when they return to their previous activity level, and whether the union of the spondylolysis affects the patients' HRQoL. A study by Miller et al. (2004) suggests that the functional outcome is good, but they did not report whether achieving bony union of the spondylolysis affects it.

6.5 HRQoL of operatively treated pediatric spondylolisthesis patients

It has been shown in earlier studies that operative treatment for pediatric spondylolisthesis improves the spondylolisthesis patients' HRQoL (Tsirikos et al 2016, Bourassa-Moreau et al 2013, Bourassa-Moreau et al. 2019). The largest study concerning this topic is a prospective multicenter study conducted by Bourassa-Moreau et al. in 2019. This study examined altogether 78 patients with an age range between 10 and 25 years, meaning that young adults were included. They showed that the SRS-22 outcomes of high-grade spondylolisthesis patients improved two years after surgery in all the domains of the SRS-22 questionnaire, whereas low-grade spondylolisthesis patients' outcomes improved only in the pain and function domains of the SRS-22 questionnaire.

Joelson et al. (2018) conducted a long-term study on the HRQoL of 38 high-grade isthmic spondylolisthesis patients three decades after fusion in situ and compared it to the HRQoL of controls. The controls were age and gender matched with spondylolisthesis patients from Swedish population based normative data for the SRS-22r. The study group established that high-grade spondylolisthesis patients have a lower score in the SRS-22r self-image and function domains three decades after surgery compared to controls. There was no correlation between severity of the

slip and SRS-22r outcome. This study also included young adults, as the age of the patients was between 9 and 24 years at the time of the surgery.

The results of study II were similar to previous studies concerning the HRQoL of operatively treated spondylolisthesis patients. In study II, the HRQoL of pediatric spondylolisthesis patients improves in the pain and activity domains of the SRS-24 two years after surgery but reaches the same level as age and sex matched controls only in the activity domain. In our study, all the patients were adolescents, as the age range was between 10 at 18 years at the time of the surgery.

6.6 Radiographic outcomes and complications of an instrumented reduction and circumferential spinal fusion for the treatment of pediatric spondylolisthesis

An earlier study by Alzakri et al. (2019) investigated pelvic balance after surgical reduction in high-grade spondylolisthesis and its relation to HRQoL. They noticed that the improvement in HRQoL was better in patients with a balanced pelvis. In their study, 27 patients had an unbalanced pelvis at baseline, and after surgical reduction, 16 of them remained unbalanced postoperatively. In study II, eight patients of the high-grade spondylolisthesis had an unbalanced pelvis prior the operation, and seven patients had it postoperatively. The patient groups of II would have been very small, and therefore the HRQoL of high-grade spondylolisthesis patients with an unbalanced pelvis and those with a balanced pelvis postoperatively were not compared with each other.

Whether reduction should be performed is a good question. On one hand, the study by Alzakri et al. (2019) noted that if with reduction a pelvic balance is achieved, it improves the HRQoL of the patient. On the other hand, Poussa et al. (2006) compared reduction for severe high-grade spondylolisthesis with in situ fusion. In their study, the in situ group had better SRS scores at the end of the follow-up time. It should be noted that in this study, cases of spondyloptosis (100% slip) were included in both groups – for a 100% slip, reduction is more susceptible to complications (Gaines et al. 2005). Longo et al. (2014) undertook a systematic review of whether reduction should be performed in a high-grade spondylolisthesis patient's operation. In their meta-analysis, neurologic deficit rates were similar in reduction (7.9%) and in situ fusion (8.9%) groups, whereas pseudoarthrosis rates were lower in the reduction group than in the in situ fusion group (5.5% vs 17.8%, respectively). In our study, the rate of postoperative radicular pain was 19% and pseudoarthrosis was 12%, so both are slightly higher than in the meta-analysis.

The most common cause for re-operation in study II was mechanical discomfort from the iliac screws in 4 (15%) of the patients. A study by Kuniyoshi et al. (2006)

proves that even though removal of the iliac screws was frequent (53% of patients), iliac screws are effective in protecting the sacral screws from failure and do not predispose patients to sacroiliac joint degeneration; moreover, the fusion rate with iliac screws is good, 96%.

6.7 Future studies

In the future, more information will be needed regarding the effectiveness of brace treatment for pediatric spondylolysis. A larger study cohort would produce statistically stronger information on this topic. A longer follow-up time of at least two years would be necessary to evaluate treatment options and development of spondylolisthesis in a longer time frame. It would be ideal to conduct a prospective randomized trial on pediatric spondylolysis, where one study group is treated with a rigid brace and the other study group is treated with a soft brace or with only restriction of sports without a brace. Yet as in our study III and in the BRAIST trial (Weinstein et al. 2013), the randomization represents a clinical challenge.

Another interesting study design for the future would be the HRQoL of pediatric spondylolysis patients with a longer follow-up time than in study III. Our study leaves me pondering on whether there would be a statistically significant difference in the HRQoL of spondylolysis patients who achieve bony union of the defect compared to the ones who do not when they return to their previous activity level.

It would also be interesting to evaluate the HRQoL of the patients of study II during a longer time period, for example ten years after the surgery. At this point, there would be a new comparison with age matched controls to determine whether operatively treated spondylolisthesis patients achieve a similar HRQoL as the normal population. The study by Joelson et al. (2018) studied patients, who underwent a fusion in situ for treatment of spondylolisthesis, for three decades after surgery – it would be interesting to see whether results are similar in patients on whom reduction of the spondylolisthesis was performed during the operation.

7 Summary/Conclusions

The results of the clinical investigations presented in this thesis give rise to the following conclusions:

6. The bony union rates of pediatric spondylolysis with a rigid thoracolumbar orthosis are 63.1% when pseudoarthrosis are disregarded from the calculations. Union rate is 84.8% for incomplete fractures and 31.1% for complete fractures.
7. An incomplete fracture in the MRI, an early stage of the defect in the CT, a high signal intake in the MRI, and unilaterality of the fracture are predictive factors for achieving bony union of pediatric spondylolysis.
8. A rigid thoracolumbar orthosis does not increase the likelihood of achieving bony union of pediatric spondylolysis when compared to an elastic, low-profile lumbar support.
9. Pediatric spondylolysis patients have equal HRQoL outcomes after treatment regardless of the brace type used for treatment of spondylolysis. When baseline HRQoL is compared with HRQoL after treatment of spondylolysis, the pain domain of the SRS-24 improves in all patients statistically significantly; additionally, the activity domain improves in patients who achieve bony union of the defect.
10. The risk of pseudoarthrosis is relatively low after instrumented circumferential spinal fusion for treatment of spondylolisthesis. In these patients, HRQoL improves but does not reach the same level as controls.

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Original Publications

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Radiographic outcomes of immobilization using Boston brace for pediatric spondylolysis.
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I

Original Research Article

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RADIOGRAPHIC OUTCOMES OF IMMOBILIZATION USING BOSTON BRACE FOR PEDIATRIC SPONDYLOLYSIS

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ABSTRACT

Background and Aims: **Spondylolysis is a common cause of lower back pain during youth. The aim of this study is to report the bony union rate and risk factors for non-union of the lumbar spondylolysis of pediatric patients treated with a rigid thoracolumbosacral orthosis (Boston brace).**

Materials and Methods: **A retrospective review of 68 children (mean age = 13.9 years) treated for spondylolysis with a thoracolumbosacral orthosis. Patient charts and imaging studies were evaluated to identify the bony union rate of the spondylolysis after a minimum of 3 months of immobilization (mean = 4.2 months). Laterality, grade, level, and presence of high signal intensity in the magnetic resonance imaging were evaluated as prognostic factors.**

Results: **Sixty-eight patients presented with 110 defects. Of them, 46 (42%) were incomplete fractures, 38 (35%) complete fractures, and 26 (24%) pseudoarthrosis. Of these defects, 38 (82.6%), 11 (28.9%), and 0 (0.0%) had bony union at the end of the treatment ($p < 0.001$). Unilateral defects healed significantly better than bilateral ones (relative risk = 1.71, 95% confidence interval = 1.16–2.54, 17/26 (65%) vs 32/84 (38%), $p = 0.014$). High signal intensity in the magnetic resonance images before the treatment predicted healing (relative risk = 13.24, 95% confidence interval = 1.93–91.01, 48/87 (55%) vs 1/24 (4.3%), $p < 0.001$). The level of the spondylolysis (L5 vs above L5) did not affect the healing rate.**

Conclusion: **The union rates of spondylolysis with a thoracolumbosacral orthosis were similar as compared to earlier studies done with a low thoracolumbosacral orthosis. The grade of the defect, laterality, and presence of high signal intensity increased the probability of bony union. A high thoracolumbosacral orthosis (underarm) does not seem to improve the healing rate of pediatric spondylolysis defects.**

Key words: Spondylolysis; pediatric; thoracolumbosacral orthosis; Boston brace

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INTRODUCTION

Lumbar spondylolysis is a common spinal disorder affecting 4.4% of children and 6% of adults (1, 2). Its etiology is typically related to a combination of congenital weakness in the pars interarticularis and mechanical stress resulting into a stress fracture (isthmic spondylolysis) (3, 4–6). Using conservative treatment, early-phase lesions may heal without development of spondylolisthesis during further growth (1, 7–9). Various methods of immobilization such as a soft corset or a low rigid overlapping orthosis have been used resulting into healing rate of 62%–94% of the early lesions, 8.7%–80% of the progressive lesions, and none of the terminal lesions (pseudoarthrosis) (7, 8–10). However, it remains unclear if the healing rates of different stages of lesions could be improved using a high rigid thoracolumbosacral orthosis which is more effective in preventing lumbar extension and flexion (11).

We aimed to report the radiographic outcomes of conservative treatment using an individualized, custom-made Boston underarm thoracolumbosacral orthosis (TLSO) for a minimum of 3 months in pediatric spondylolysis. We hypothesized that a high TLSO management would heal the majority of early-phase isthmic lesions while more advanced lesions would heal less often.

MATERIALS AND METHODS

PATIENTS

A retrospective review of our academic medical center database identified 76 consecutive patients with unilateral or bilateral spondylolysis who were treated with a TLSO (Boston underarm brace) between 2010 and 2018. Inclusion criteria included age under 18 years at the time of the diagnosis, uni- or bilateral spondylolysis treated with a rigid TLSO targeting to bony healing. Exclusion criteria included high energy trauma, systemic illness potentially affecting bony healing or bone density (osteogenesis imperfecta, skeletal dysplasia, primary or secondary osteoporosis or endocrine disorder, that is, hypothyreosis). Of the 76 patients, 8 were excluded from the analyses: 4 patients did not have a fracture line (only a stress reaction in the pars interarticularis); 1 patient had a stress fracture in the sacrum; 1 patient did not have magnetic resonance (MR) images before the treatment; and 2 patients did not have computed tomography (CT) or MR images after the treatment to evaluate bony healing. Thus, 68 patients were included in this study. These patients' medical history was re-examined, and the imaging studies of these patients were re-evaluated by an independent musculoskeletal radiologist. The aims of this retrospective study were to investigate the bony union rate of the spondylolysis with a rigid TLSO and to find out factors affecting the bony healing.

The 68 patients (mean age = 13.9 years, range = 6.3–17.8 years, 36 (53%) males) with spondylolysis were immobilized with a rigid TLSO (Boston underarm brace) for a minimum of 3 months (mean = 4.2 months, range = 1.4–5.6 months). All (100%) of the patients were active in sports. The most common sport was soccer (26 patients), followed by ice hockey (12 patients), gymnastics (8 patients), and figure skaters (2 patients). All of the spondylolysis were confirmed with magnetic resonance imaging (MRI) in the beginning of the treatment, an additional CT before immobilization was taken from 27 (39.7%) patients, and the plain radiographs were taken from 31 (41.6%) patients. The spondylolysis was noted in these radiographs in 13 (41.9%) patients. Of these 68 spondylolysis, 26 (38.2%) were unilateral and 42 (61.8%) were bilateral. Therefore, a total of 110 defects were seen in these 68 patients. Twenty (18%) of the defects were above L5 (2 in L1, 4 in L3, and 14 in L4 vertebra) and 90 (82%) in the L5 vertebra. The majority of the lesions above L5 were bilateral: only two (10%) of them were unilateral. The fractures were classified into three grades (incomplete fracture/complete fracture/chronic defect = pseudoarthrosis) by an independent musculoskeletal radiologist according to Hollenberg et al.'s (12) MRI grading system. Stress reactions were only reported when they occurred along with a defect elsewhere.

The treatment consisted of restriction on all exercise except walking and a rigid TLSO (Boston underarm brace). Patients were advised to wear the orthosis 23 h a day. The mean immobilization time was 4.2 months ranging from 1.4 to 5.6 months. At the end of the treatment, either MR images (33 patients) or CT images (24 patients) or both (11 patients) were used to evaluate bony healing of the pars defect. In patients with both examinations, the bony healing was evaluated using the CT images.

STATISTICAL ANALYSES AND ETHICAL COMMITTEE APPROVAL

Statistical comparisons were performed with chi-square tests for categorical parameters and unpaired t-tests for continuous variables. p-values of 0.05 or less were considered significant. Relative risks (RRs) and their 95% confidence intervals (CIs) were calculated with the bilateral spondylolysis and no high signal intensity used as the reference.

Ethical committee approval was granted by Turku University Hospital. Due to retrospective nature of the research, no informed consent was requested by the ethical committee.

RESULTS

The main characteristics of the defects and their bony union rates are shown in Tables 1 and 2. There were 46 (41.8%) incomplete fractures, 38 (34.5%) complete fractures, and 26 (23.6%) pseudoarthrosis in 68 patients. Sixty-seven (98.5%) of the patients followed up the recommended treatment protocol. Of these defects, 38 (82.6%), 11 (28.9%), and 0 (0.0%) had a bony union at the end of treatment, respectively ($p < 0.001$). Unilateral defects healed significantly better than the bilateral ones (RR = 1.71, 95% CI = 1.16–2.54, 17/26 (65%) vs 32/84 (38%), $p = 0.014$). High signal intensity of the pars interarticularis in the MR images before the treatment also predicted healing (RR = 13.24, 95% CI = 1.93–91.01,

TABLE 1
Clinical characteristics of the study groups based on the laterality.

	Unilateral (n = 26)	Bilateral (n = 42)	Significance
Age at the beginning of immobilization (years)	14.1 (6.6–17.8)	13.7 (6.3–16.8)	0.42[b]
Males/Females	13/13	23/19	0.70[a]
Body Mass Index	20.6 (17.2–27.4)	20.9 (14.4–31.6)	0.80[b]
Grade of the fracture (right/left)			
Stress reaction	5/1	0/0	0.021[a]
Incomplete	6/10	16/14	
Complete	3/5	14/16	
Pseudoarthrosis	1/1	12/12	
Level of injury, n			
L1	0/26 (0%)	21/42 (2%)	0.13[a]
L3	0/26 (0%)	2/42 (5%)	
L4	2/26 (7%)	6/42 (14%)	
L5	24/26 (93%)	33/42 (79%)	
Preoperative imaging modality			NA
MR image	26/26	42/42	
CT	10/26	17/42	
Standing radiograph	10/26	20/42	
Immobilization (months)	4.2 (1.4–5.6)	4.2 (2.6–5.6)	0.90[b]
Follow-up imaging modality			
MR image	18/26	26/42	NA
CT	14/26	21/42	

NA: not applicable; MR: magnetic resonance; CT: computed tomography.
[a]Categorical variables were compared using the χ^2 test.
[b]Continuous variables were analyzed using the unpaired t-test.

TABLE 2
Bony union rates in different groups.

n = 110 defects	Number with union/total (%)	p-value[a]
Grade of the pars defect		
Incomplete fracture	38/46 (82.6)	<0.001
Complete fracture	11/38 (28.9)	
Pseudoarthrosis	0/26 (0.0)	
Vertebral level		
Above L5	8/20 (40.0)	0.12
L5	41/90 (45.6)	
Laterality		
unilateral	17/26 (65.3)	0.014
bilateral	32/84 (38.1)	
High signal intensity in MRI		
No	1/23 (4.3)	<0.001
Yes	48/87 (55.2)	

MRI: magnetic resonance imaging.
[a]Variables were compared using the χ^2 test.

48/87 (55%) vs 1/24 (4.3%), $p < 0.001$). The level of the spondylolysis (L5 vs above L5) did not affect the healing rate. The effects of level of the lesion, uni- versus bilateral, and stage of the lesion are shown in Fig. 1. This figure demonstrates that the level of the lesion does not affect the healing rate when uni- versus bilaterality and the stage of the lesions are evaluated. Fifty-eight (85%) out of the 68 patients were asymptomatic at the end of immobilization.

DISCUSSION

VALIDITY OF THE DATA

The study was conducted as a retrospective consecutive series. The radiographic analyses were conducted blinded by an independent observer (A.S.). We consider the number of patients (n = 68) to be satisfactory. Follow-up time was 3 months, and our aim was to evaluate bony healing at the end of the treatment. Some of patients may develop a recurrence of the spondylolysis and those not healing a spondylolisthesis during longer follow-up. We did not obtain standing radiographs at the end of immobilization. Bony healing was evaluated using advanced imaging (CT or MR images) done at the end of immobilization in all patients. The correlation of these investigations was generally good. Before treatment, there were two fractures that were classified as incomplete fracture in the MRI and classified as progressive lesions in the CT, while the rest of the incomplete fractures (20 fractures) were also classified as early lesions in the CT. There were two stress reactions seen in the MRI and one did not visualize in the CT. All of the lesions which seemed to be pseudoarthrosis in the MRI were classified as terminal lesions in the CT as well as all of the fractures that were classified as complete fractures in the MRI were graded as progressive lesions in the CT.

After the treatment, there were 11 patients of which both the MRI and CT were taken after the treatment to evaluate the bony healing of the fracture. In one case, the MR image suggested that no bony healing was obtained, while CT showed bony bridges over the

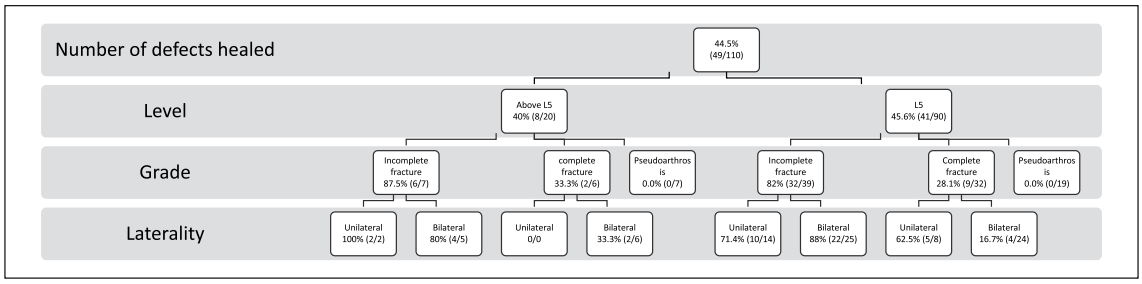

Fig. 1. Bony union rates of different skeletal levels, stage of the fracture, and laterality.

fracture line. In the rest of these patients, the CT and the MRI findings correlated well. The patients were advised to wear the Boston brace 23 h a day, but we did not have a sensor in the brace to record the actual use of the orthosis.

Ideally, the effect of high thoracolumbosacral orthosis on the healing rate of pediatric spondylolysis should be confirmed in a randomized clinical trial. However, conducting such a high-level trial is very challenging. For example, the majority of the patients in the Bracing in Adolescent Idiopathic Scoliosis Trial (BRAIST) (13)—comparing the effect of such an orthosis on the progression risk of adolescent idiopathic scoliosis—chose themselves which treatment observation or brace they wanted and the randomized trial arm was ended well before the inclusion requirement was fulfilled.

COMPARISON WITH PREVIOUS STUDIES

Spondylolysis is a common cause of back pain in the adolescence, seen in 47% of young athletes complaining lower back pain (14). The bony union of the spondylolysis depends on several factors. The grade of the fracture seems to be an important factor affecting the probability of the union (8–10). The unilaterality and the high signal intensity seen in the MRI prior the treatment seem to increase the probability of osseous healing (9).

Various kinds of rigid orthosis have been used for the treatment of pediatric spondylolysis. In the meta-analysis done by Klein et al. (15), bracing did not seem to affect the clinical outcome of the patients after minimum 1-year follow-up. We could still hypothesize that the higher the bony union rate of spondylolysis, the less lower back problems the patients may have in the long run. Many studies have shown good outcomes with different kinds of braces for the treatment of the spondylolysis. Fujii et al. (8) studied the union rates of 239 spondylolysis defects using a soft Damen corset. The union rate for early lesions was 62%, for progressive lesions 8.7% and for terminal lesions (pseudoarthrosis) 0%. In this study, they also noticed that the L4 spondylolysis had a higher union rate (62.9%) compared to the L5 fractures (8.8%). In our study, the level of the affected vertebra did not have an impact on the union rate and this is not in agreement with the earlier findings by Fujii et al. (8) study, and therefore, further investigations of this subject are needed.

Sairyo et al. (9) used a low hard lumbar brace for immobilization (mean time of immobilization varied from 3.2 months for early and 5.7 months for progressive with low signal intensity group) and noted a bony union in 94% of the early defects, 46% of the progressive-stage defects, and in 0% of the terminal defects. In their study, the treatment time was lengthened up to 6 months if bony healing was not considered to be strong enough after 3 months. In the study of Sakai et al. (10), a low thoraco-lumbo-sacral-type trunk brace (Sairyo-model hard corset) was used to immobilize the patients. They had quite small sample size with only 23 patients with either early or progressive defects (27 had either a stress reaction only or 10 patients a terminal defect) with healing rates 93.8% of the early defects and 80.0% of the progressive defects. In this study, 38 (82.6%) of the early defects, 11 (28.9%) progressive, and none (0.0%) of the terminal defects had a bony union at the end of treatment. Thus, based on this study, a high TLSO does not seem to provide additional benefits as compared with a low rigid brace. Therefore, further studies comparing different kind of braces for the treatment of spondylolysis will be needed to optimize the treatment.

In accordance with the previous studies done by Fujii et al. (8), Sairyo et al. (9), and Sakai et al. (10), none of the pseudoarthrosis/terminal defects had bony union after brace treatment in our study. In this study, the majority of the patients (74%, 14/19) were pain-free after brace treatment. Therefore, the goal of the treatment of the terminal spondylolysis should not be bony healing, but an asymptomatic patient using, for example, a suitable sporting activity level and not a formal immobilization.

CONCLUSION

Unilaterality, incomplete fracture, and lesions with high signal intensity on MR images predicted healing of pediatric spondylolisthesis. A 3-month immobilization using a high rigid thoracolumbosacral orthosis resulted into following healing rates: 83% of incomplete, 29% of the complete, and 0% of the pseudoarthrosis had a bony union at the end of treatment.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or

publication of this article: I.H. is a consultant for Medtronic. He has received research grants and funding from Medtronic International and K2M via Innosurge. E.V. has received a research grant from Clinical Research institute HUCH. M.H., K.M., and O.P. declare that they have no conflict of interest.

ETHICAL APPROVAL

Ethical committee approval was granted by Turku University Hospital. Due to retrospective nature of the research no informed consent was requested by the ethical committee.

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INFORMED CONSENT

This study was a retrospective study and therefore no informed consent was obtained. Individual patients cannot be identified.

RESEARCH ETHICS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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II

Spine

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CLINICAL CASE SERIES

Health-Related Quality of Life Outcomes of Instrumented Circumferential Spinal Fusion for Pediatric Spondylolisthesis

A Comparison With Age and Sex Matched Healthy Controls

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Study Design. A prospective study on the clinical, radiographic, and the health-related quality of life (HRQOL) outcomes in adolescents with spondylolisthesis undergoing instrumented circumferential spinal fusion compared with age and sex matched controls.

Objective. To determine the outcomes of pediatric spondylolisthesis patients minimum 2 years after surgery and to compare their HRQOL with age and sex matched controls.

Summary of Background Data. There is limited evidence of the HRQOL of adolescent spondylolisthesis patients after surgery and no studies comparing it with healthy controls.

Methods. Twenty-six consecutive adolescents (mean age 14.7 yr, range 10–18 yr) undergoing instrumented reduction with intercorporeal spinal fusion for spondylolisthesis (11 low-grade, 15 high-grade) by a single orthopedic surgeon were included to this study cohort and matched by age and sex with two controls. The HRQOL was measured with Scoliosis Research Society-24 (SRS-24) questionnaire before surgery, 6 months and 2 years after the surgery.

Results. The mean (SD) vertebral slip in the low-grade patients was 25% (13%) and 67% (15%) in the high-grade patients and 6% (7%) and 21% (25%) postoperatively, respectively ($P \leq 0.041$ for both comparisons). Three (12%) patients developed a non-union during follow-up. None of the patients developed a persistent neurologic deficit, but two (8%) patients presented with chronic postsurgical pain persisting 24 months. Seven (27%) of the patients had reoperations for any reason during the follow-up. Pain and activity domains of the SRS-24 improved significantly from preoperative to 2-year follow-up ($P \leq 0.007$ for both). SRS pain, self-image, function domains, and total score were significantly worse as compared with the 52 controls ($P \leq 0.020$ for all comparisons).

Conclusion. Risk of non-union is relatively low after instrumented spinal reduction in adolescents with spondylolisthesis. HRQOL improves significantly after instrumented reduction and circumferential spinal fusion in adolescents with spondylolisthesis, but remains at statistically lower level than in the controls.

Key words: adolescent spondylolisthesis, health-related quality of life, outcome, SRS-24.

Level of Evidence: 2

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Spondylolisthesis is one of the most common causes of low back pain and radicular symptoms in the adolescent population.[1,2] It is divided in low-grade and high-grade spondylolisthesis according to Meyerding classification: a vertebral slip on a sagittal lumbar radiograph less than 50% (Meyerding I–II) is low-grade and a slip over 50% (Meyerding III–V) is high-grade.[3,4] Low-grade spondylolisthesis is treated with pain medication, restriction of sports, and operated only if there is persistent pain after conservative treatment.[5–8] In pediatric high-grade spondylolisthesis, an operative treatment with a short posterolateral fusion has been suggested due to the risk of slip

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progression and higher degree of symptoms.[8–11] Instrumented reduction seems to improve fusion rate as compared with in situ fusion,[12] although the long-term health-related quality of life has been better with circumferential in situ fusion than with reduction.[13]

Previous smaller studies have suggested improvement in the health-related quality of life (HRQOL) after spinal fusion in children with spondylolisthesis,[14,15] but guidance is limited in children as the largest series included also young adults.[16] The latter multicenter study showed improvement in the HRQOL in all the areas of SRS-22 questionnaire after the surgery in majority of patients, especially in the high-grade spondylolisthesis patients.

In this study we aimed to examine whether the HRQOL improves in children after operative treatment for spondylolisthesis using an instrumented reduction and circumferential spinal fusion. We also wanted to compare the HRQOL in these children with age and sex matched healthy controls and whether there is a difference in the HRQOL between operatively treated low-grade and high-grade spondylolisthesis patients. The hypothesis was that the HRQOL improves after surgery, is better in low-grade spondylolisthesis patients compared with high-grade spondylolisthesis patients and is at similar level in these patients as compared with the healthy controls.

MATERIALS AND METHODS

Patients

Twenty-six consecutive patients aged between 10 through 18 years with operatively treated spondylolisthesis were prospectively included from May 2009 to November 2017 in this study. All of the patients had pedicle screw instrumentation with intercorporeal fusion using TLIF cage or autologous structural bone graft. Neural elements were widely decompressed for nerve roots (L5, S1) and cauda equinae. Reduction of the vertebra was performed in all patients expect for the one with spondyloptosis (slip 100%) who underwent transsacral instrumentation and bone grafting in situ. Patients with low-grade spondylolisthesis had pedicle screws inserted into L5 and S1 to reduce the spondylolisthesis and patients with high-grade spondylolisthesis underwent instrumentation from L4 to S1 with iliac or S2AI screws.[17–20] Transforaminal lumbar intercorporeal fusion cage was inserted in addition to standard posterolateral spinal arthrodesis. All patients were operated by a single orthopedic spine surgeon (IH) and had a minimum 2-year follow-up.

Outcome Parameters

Clinical and radiographic was collected prospectively preoperatively, at 6 months, and at 2 years follow-up. The HRQOL was analyzed using Scoliosis Research Society-24 (SRS-24) outcome questionnaire.[21] The follow-up time in all patients was a minimum of 2 years (mean 3.3 yr, range 2–10 yr). Perioperative data as in operation time, blood loss, and levels of instrumentation were collected. Radiographic outcome was assessed from a standing radiographs of the spine. Standing spinal radiographs were taken prior to operation, 6 months and 2 years after the operation. Of these radiographs the percentage slip of the vertebra, lumbosacral angle, pelvic incidence, pelvic tilt, sacral slope, and lumbar lordosis (T12–S1) were measured as radiographic parameters.[22] The high-grade spondylolisthesis patients were divided into balanced and unbalanced groups.[23,24] For follow-up visits, the status of the instrumentation was evaluated (intact, broken screws or rods, signs of loosening). A routine computed tomography (CT) scan was not obtained to evaluate spinal union at the final follow-up.

Healthy Controls

Healthy controls were obtained from our previous population based study in which healthy adolescents and adults were asked to fill out a modified version of the original SRS health-related quality of life questionnaire (SRS-24)[21]: the SRS-22r questionnaire.[25,26] In this study 272 healthy controls were selected from a population register and were invited to complete and return the SRS-22r questionnaire between January 2012 and December 2015. Two controls from this cohort were matched with each patient for age (±2 yr) and sex. Age matching was done with the age of the surgically treated patients in their last follow-up.

Scoliosis Research Society Outcome Questionnaire

The SRS-24 is the original disease specific questionnaire developed by the Scoliosis Research Society.[21] It originally measured and evaluated the HRQOL in operatively treated patients with adolescent idiopathic scoliosis. However, it has been broadly accepted and used to evaluate the HRQOL in patients treated operatively for other spinal problems as well, including pediatric lumbar spondylolisthesis.[27–29] The SRS-24 questionnaire consists of 24 questions concerning seven domains: pain, general self-image, function from back condition, general level of activity, postoperative self-image, postoperative function, and satisfaction. Every question is scored from one to five and the maximum score of this questionnaire is 120. The higher the score, the better the outcome. The questions from 16 to 24 concern the treatment and can therefore be filled out posttreatment only.

SRS-22r is an improved version of the SRS-24 questionnaire. Its questions are either exactly the same or close to the original SRS-24 questionnaire questions. In our study the control group members had filled SRS-22r questionnaire. Because the control group were healthy individuals without any treatment, only questions 1 to 15 from the original SRS-24 (preoperative domains) were used and compared with the similar questions of the SRS-22r (questions 1, 2, 4, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 19, 20 from the SRS-22r). The domains were formed as follows: pain (SRS-24: 1, 2, 3, 6, 8, 11; SRS-22r: 1, 2, 4, 8, 11, 14), general self-image (SRS-24: 5, 14, 15; SRS-22r: 6, 19, 20), general function (SRS-24: 7, 12, 13; SRS-22r: 9, 15, 18), and general activity (SRS-24: 4, 9, 10; SRS-22r: 5, 12, 17).[30,31] There are eight exactly the same questions with exactly similar options in the SRS-24

and the SRS-22r and these questions were also compared across the groups (SRS-24: 1, 2, 3, 4, 5, 6, 7, 8; SRS-22r: 1, 2, 4, 5, 6, 8, 9, 11).

Statistical Analysis

Statistical comparisons of radiographic parameters were performed with unpaired *t* tests. Linear mixed models for repeated measures analysis were used to study the variation of SRS domains over time. We log transformed the mirror transforms of the domain scores prior to analysis in order to prevent left skew in the residuals of those models. We applied the Kruskal–Wallis test on the original domain scores to compare patients with controls. The *P*-values in pairwise comparisons were adjusted for time. Significance level was at <0.05.

Ethical Committee Approval

Ethical committee approval was obtained from local ethical boards. For the spondylolisthesis patients ethical committee did not request informed consent as they underwent clinically standardized treatment protocol without additional examinations. Written informed consent was acquired from the normative population and if needed from their guardians.

RESULTS

A total of 26 consecutive adolescents (mean [SD] age at the time of surgery 14.7 yr [±1.9 yr]) who underwent operative treatment for spondylolisthesis were included in this study (Table 1). Eleven (42%) of the patients had low-grade and 15 (58%) had a high-grade slip. One of the high-grade spondylolisthesis was spondyloptosis (slip 100%, Meyerding V). The indication for surgery was either a low-grade slip with ongoing symptoms after a year of conservative treatment or a high-grade spondylolisthesis. Conservative treatment consisted of restriction of sports, pain medication, and in some cases brace treatment to relief the pain. Associated pain scoliosis was seen in two (18%) patients with a low-grade spondylolisthesis and in 10 (67%) patients with a high-grade spondylolisthesis (Table 2). In these patients the lumbar scoliosis resolved after spinal fusion for spondylolisthesis. Therefore, we assumed this deformity to be part of the deformity itself or the pain component of the spondylolisthesis. Additionally, idiopathic scoliosis was found in three (27%) patients in the low-grade spondylolisthesis group and six (40%) patients in the high-grade spondylolisthesis group. Two patients with a high-grade spondylolisthesis had earlier undergone spinal arthrodesis for adolescent idiopathic scoliosis.

Seventeen (65%) of the patients were asymptomatic at the end of the follow-up and did not develop any complications.

Radiographic Outcome

The mean preoperative slip in the low-grade patients was 25% (±13%) and 67% (±15%) in the high-grade patients (Table 2). After instrumented reduction the mean slips were 6% (±7%) and 21% (±25%), respectively. Similarly, the lumbosacral angle remained at 10° pre- and postoperatively in the low-grade group, but improved from 14° (±11°) to 10° (±6°) in the high-grade group. Unbalanced pelvis occurred preoperatively in eight (53%) of the high-grade patients and in seven (47%) at 2-year follow-up (N.S.). An example of patient's radiographs prior and after the operation are seen in Figures 1 and 2Figures 1A, B and 2A, B.

Complications

Three (12%) patients had a cerebrospinal fluid leak during surgery, which was noted and closed during the primary operation without further events. None of the patients developed a persistent neurologic deficit, but five (19%) patients had radicular pain at least occasionally postoperatively during the follow-up time. Two (8%) of these patients presented with chronic postsurgical pain persisting 2 years. Seven (27%) of the patients had reoperations for any reason during the follow-up time. Three (12%) of the patients (one with low-grade and two with high-grade slip) developed a pseudoarthrosis, two of them have undergone a revision procedure, one of them twice (5 and 8 yr after the primary operation). One (4%) patient developed spondylolisthesis at

TABLE 1. Clinical Characteristics

Variable	Spondylolisthesis Patients (n = 26)	Healthy Controls (n = 52)
Age at 2-year FU, year	16.7 ± 1.94	17.6 ± 3.8
Gender (male)	23% (6/26)	23% (12/52)
FU time, year	3.3 ± 1.75	
Amount of slip		
Low grade (0–50%)	42% (11/26)	
High grade (51–100%)	58% (15/26)	
Levels fused		
L5–S1	46% (12/26)	
L4–S1	54% (14/26)	
Blood loss, mL	391 ± 185	
Operative time, hour	3.8 ± 1.3	

Scores are mean values and SD.
FU indicates follow-up.

TABLE 2. Radiographic Parameters of the Study Groups

Radiographic Parameters	Low-Grade (n = 11)	High-Grade (n = 15)	*P* Value
Slip (%)			
Preoperative	25% ± 13%	67% ± 15%	<0.001
2-year FU	6% ± 7%	21% ± 25%*	0.041
Lumbosacral angle			
Preoperative	10° ± 8°	14° ± 11°	0.322
2-year FU	10° ± 8°	10° ± 6°	0.884
Pelvic tilt			
Preoperative	18° ± 9°	30° ± 8°	0.004
2-year FU	20° ± 5°	26° ± 8°	0.044
Sacral slope			
Preoperative	44° ± 12°	46° ± 8°	0.628
2-year FU	40° ± 13°	46° ± 6°	0.164
Unbalanced pelvis			
Preoperative	N/A	57% (8/14)	
Postoperative	N/A	47% (7/15)	
Pelvic incidence	60° ± 10°	72° ± 10°	0.007

**In the high-grade group one patient had spondyloptosis (100% slip) and no reduction of the slip was performed in the operation.*
Scores are mean values and SD.

the level above the index procedure (L4–5) necessitating fusion over this level 8 months after the primary operation. Four (15%) patients had mechanical discomfort from the iliac screws and they were later removed. In one of these four patients a persistent postoperative cerebrospinal spinal fluid leakage required a re-revision to seal the leak. There were no deep surgical site infections.

Quality of Life and SRS Scores in Surgically Treated Spondylolisthesis Patients

Twenty-two (85%) patients completed the SRS-24 questionnaire preoperatively and twenty-three (88%) patients filled the same questionnaire 2 years after the surgery. The SRS-24 pain and activity domains improved significantly from preoperative to 2-year follow-up ($P \leq 0.007$ for both) (Table 3). With the exception of postoperative function and satisfaction, the scores of the SRS-24 questionnaire were higher for high-grade spondylolisthesis patients than for low-grade spondylolisthesis patients, but only the difference in the self-image domain was significant ($P = 0.008$, results not shown).

Comparison of Quality of Life and SRS Scores in Operatively Treated Spondylolisthesis Patients and Controls

The SRS scores in pain, self-image, and function domains and the total SRS score were significantly lower in the

Figure 1. A and **B**. A 15-year-old boy with a high-grade spondylolisthesis (slip 58%). (**A**) Posteroanterior and lateral (**B**) standing lumbar spine radiograph.

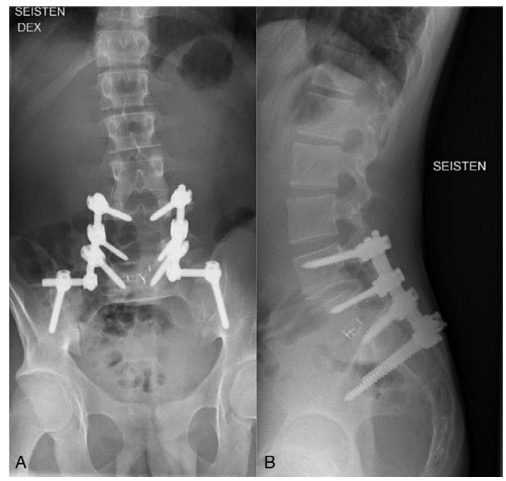

Figure 2. A and **B**. The same patient as in the Figure 1 2 years after L5 and S1 nerve root decompression and circumferential spinal fusion with instrumented reduction from L4 to S1 with iliac screws.

TABLE 3. The Changes in SRS-24 Outcome Questionnaire

SRS Domain	Preoperative (N = 22)	6 Months Follow-up (N = 20)	2-Year Follow-up (N = 23)	*P* Value
Total	3.59 ± 0.61	3.82 ± 0.52	3.86 ± 0.68	0.059*
Pain	3.27 ± 0.93	4.24 ± 0.89	3.92 ± 1.03	0.007*
Self-image	4.03 ± 0.63	4.11 ± 0.39	4.28 ± 0.57	0.052*
Function	3.85 ± 0.50	3.96 ± 0.52	4.10 ± 0.46	0.065*
Activity	3.53 ± 1.06	3.81 ± 1.18	4.22 ± 1.25	0.001*
Postop self-image	N/A	3.18 ± 0.57	3.26 ± 0.67	0.627†
Postop function	N/A	2.42 ± 1.17	3.00 ± 1.41	0.072†
Satisfaction	N/A	4.02 ± 0.60	3.91 ± 0.56	0.260†

*2-year follow-up scores compared with preoperative scores.
†2-year follow-up scores compared with 6 months follow-up scores.
Scores are mean values and SD. SRS-24 indicates Scoliosis Research Society-24.

surgically treated spondylolisthesis patients at their 2-year follow-up visit than in the age and sex matched controls ($P < 0.05$ for all comparisons, Table 4). The spondylolisthesis patients reached controls only in the activity domain during the 2-year follow-up time. When low-grade and high-grade spondylolisthesis patients where separately compared with controls it was noted that the low-grade spondylolisthesis patients had statistically significantly lower scores in pain ($P = 0.002$), self-image ($P = 0.027$), and function ($P < 0.001$) domains. The high-grade spondylolisthesis patients had statistically significantly lower scores in the pain ($P = 0.020$) and the function ($P < 0.001$) domains (Table 5).

DISCUSSION

To the best of our knowledge, this is the first prospective study comparing the HRQOL of the operatively treated

TABLE 4. Comparison of SRS Outcomes Between Surgically Treated Patients and Age and Sex Matched Controls

SRS Domain	2-Year Follow-up (n = 23)	Healthy Controls (n = 52)	*P* Value
Total*	4.10 ± 0.76	4.73 ± 0.33	<0.001
Pain†	3.97 ± 1.02	4.76 ± 0.45	<0.001
Self-image	4.28 ± 0.57	4.57 ± 0.50	0.018
Function	4.09 ± 0.46	4.91 ± 0.19	<0.001
Activity	4.22 ± 1.25	4.66 ± 0.46	0.482
Total of eight same questions	4.03 ± 0.89	4.67 ± 0.41	<0.001

*2-year follow-up SRS scores excluding the questions regarding postoperative state.
†The postoperative pain question is excluded.
Scores are mean values and SD.

TABLE 5. Comparison Between SRS Domains in the Low-Grade *Versus* High-Grade Slips and Healthy Controls

SRS Domain	Low-Grade 2-Year Follow-up (n = 10)	Healthy Controls (n = 52)	*P* Value*	High-Grade 2-Year Follow-up (n = 13)	*P* Value†
Total‡	3.81 ± 0.95	4.73 ± 0.33	<0.001	4.33 ± 0.51	0.002
Pain§	3.68 ± 1.25	4.76 ± 0.45	0.002	4.19 ± 0.79	0.020
Self-image	4.13 ± 0.55	4.57 ± 0.50	0.027	4.38 ± 0.59	0.457
Function	3.88 ± 0.62	4.91 ± 0.19	<0.001	4.26 ± 0.20	<0.001
Activity	3.67 ± 1.54	4.66 ± 0.46	0.150	4.64 ± 0.81	0.816
Total of eight same question	3.74 ± 1.05	4.67 ± 0.41	0.009	4.26 ± 0.69	0.067

Scores are mean values and SD.
*Low-grade SRS-24 2-year follow-up versus healthy controls SRS-22.
†High-grade SRS-24 2-year follow-up versus healthy controls SRS-22.
‡2-year follow-up SRS scores excluding the questions regarding postoperative state.
§The postoperative pain question is excluded.

spondylolisthesis patients with age and sex matched controls. Our study shows that the HRQOL improves in pain and activity domains in spondylolisthesis patients after surgery but reaches equal level compared with healthy controls only in the activity domain. Surprisingly, the low-grade spondylolisthesis patients had lower values in all the domains expect for the activity of the SRS questionnaire than the healthy controls, whereas the high-grade spondylolisthesis patients had lower values only in the pain and function domains.

Comparison With Previous Data

In previous studies, the HRQOL has improved after surgical treatment for pediatric spondylolisthesis.[14–16] Bourassa-Moreau *et al*[15] published a study 2013 where they measured HRQOL of the conservatively treated and the surgically treated high-grade spondylolisthesis patients during 2-year follow-up. In their study there were 23 patients in the surgically treated group and only five patients in the conservatively treated group. The decision of the surgical treatment was not standardized but left for the treating surgeon. The age of the patients was between 10 and 20 years at initial presentation. In their study the HRQOL improved in all the domains of SRS-22 for the surgically treated high-grade spondylolisthesis patients and stayed the same in the conservatively treated high-grade spondylolisthesis patients. They did not compare the HRQOL in conservatively *versus* surgically treated patients. Tsirikos *et al*[14] examined fusion rates and the HRQOL of the low-grade spondylolisthesis patients who failed the conservative treatment and went through in situ posterolateral arthrodesis without instrumentation. In their study all 36 adolescent patients (aged between 9.8 and 17.3 yr) had spinal fusion but the pars interarticularis fracture (spondylolysis) persisted at least in one side in most of the patients. In their study the HRQOL improved statistically significantly in all the domains of the SRS questionnaire following surgery.

In a prospective multicenter study done by Bourassa-Moreau *et al*[16] the HRQOL of the surgically treated spondylolisthesis patients improved in all the domains of the SRS-22 questionnaire 2 years after the surgery compared with the SRS-22 prior the surgery. In their study young adults were included to the study cohort, as the age limit was between 10 and 25 years at surgery. When comparing separately low-grade and high-grade spondylolisthesis patients, the pain and function domains of the low-grade spondylolisthesis patients improved after surgery whereas in high-grade spondylolisthesis patients all of the domains improved statistically significantly after surgical treatment for spondylolisthesis. In their study indication for surgery and technique of the surgical intervention were left to the decision of the surgeon. In a long-term study patients fused in situ for high-grade spondylolisthesis had a similar pain and mental health SRS scores as compared with healthy controls, while self-image and function scores were significantly lower, but the difference in means was small.[32] In the current study the pain and activity domains improved from preoperative to 2-year follow-up in the surgically treated adolescents. Despite improvement, the SRS total score, pain, self-image, and function domains remained at significantly lower level at the end of follow-up than in controls.

Seven (27%) of the patients underwent re-operation during follow-up. Two of these were due to non-union, one had junctional issue necessitating extension of instrumentation, and four patients required removal of symptomatic iliac screws. In an evidence-based review of spondylolisthesis, Longo *et al*[12] observed pseudoarthrosis in 5.5% of 165 patients undergoing reduction as compared with 17.8% of 101 undergoing fusion in situ. The risk of non-union (12%) in the current series after instrumented reduction and circumferential spinal fusion was higher than in this review. Iliac screw augmentation of S1 pedicle screws has improved the fusion rate of high-grade spondylolisthesis.[20] In accordance with our study, however, a large number of their patients (53%) also required symptomatic iliac screw removal.

Carreon *et al*[33] have defined the minimum clinically important difference (MCID) for the SRS-22r questionnaire for appearance/self-image, activity, and pain domains after surgical correction of adolescent idiopathic scoliosis. In this study the MCID for the pain domain was 0.20, 0.08 for the activity domain, and 0.98 for the appearance domain. There are no similar definitions to surgically treated children with spondylolisthesis. In our study the improvement was 0.68 in the pain, 0.19 in the self-image, and 0.89 scores in the activity domain. Improvements in the pain and activity domains are significantly above the MCID levels as defined for operatively treated scoliosis patients and it can be assumed that the changes in these domains are over the minimum clinically important difference also in the spondylolisthesis patients. In our previous study adolescents operated for adolescent idiopathic scoliosis (AIS) had similar scores of the SRS-24 domains except for the function domain at 5-year follow-up compared to age and gender matched controls.[28] We hypothesize that pain may have more pronounced effect on health-related quality of life than pure spinal deformity does.

Limitations and Strengths

Children needing surgical treatment for spondylolisthesis are relatively rare even in an academic pediatric spine unit. Thus, the number of surgically treated patients was relatively small. One limitation of this study was the somewhat different questionnaires used (the SRS-24 and SRS-22r). However, we chose to keep the same original SRS-24 questionnaire in the surgical treatment group in order to provide data from preoperative to minimum 2 years follow-up. We used the 15 most similar preoperative questions from the SRS-24 and SRS-22r to provide comparable questionnaires, including eight questions that were exactly the same. With these questions we formed the pain, activity, self-image, and function domains of SRS-24. The strengths of

this study include a comparison with an age and sex matched healthy control group consisting of two matched controls to each surgically treated spondylolisthesis patient. This is a prospective, consecutive cohort study, where the indications for surgery were clear. All the patients were operated using a similar surgical technique by a single orthopedic spine surgeon. The follow-up time was a minimum of 2 years. The SRS-24 questionnaire used in this study is standardized, validated, and widely used.

CONCLUSION

In conclusion, the SRS-24 scores in pain and activity domains improved statistically significantly after the surgery for spondylolisthesis during 2-year follow-up time. However the scores in pain, self-image, and function domains were significantly lower as compared with age and sex matched healthy controls.

➢ Key Points

- ❑ HRQOL improves significantly after instrumented reduction and circumferential spinal fusion in adolescents with spondylolisthesis.
- ❑ HRQOL remains at statistically lower level at 2-year follow-up than in healthy age and sex matched controls.
- ❑ Risk of non-union is relatively low after instrumented spinal reduction in adolescents with spondylolisthesis.

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III

Elastic Lumbar Support versus Rigid Thoracolumbar Orthosis for Acute Pediatric Spondylolysis. A Prospective Follow-Up Study

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Abstract (250 words)

Objectives. To compare rigid thoracolumbar orthosis to elastic lumbar support in treatment of acute pediatric spondylolysis in terms of bony union and health-related quality of life (HRQoL) at four months.

Methods. Fifty consecutive children aged 10 to 17 years with acute spondylolysis were prospectively enrolled. Patients were treated with a rigid thoracolumbar orthosis (Boston brace) or with an elastic lumbar support. First 14 patients were randomized and the remaining 36 chose brace type themselves. All patients had restriction of sports for the treatment time of four months. Treatment outcomes included bony union of spondylolysis in CT at 4 months and HRQoL using the SRS-24 outcome questionnaire before and after the treatment.

Results. Out of the 50 patients, 48 completed the treatment protocol. Twenty-eight patients were treated using Boston brace and 20 patients using elastic lumbar support. Difference in union rates was not significant as union was obtained in 71.4% (20/28) of Boston brace and in 75.0% (15/20) of elastic lumbar support group patients (RR 1.14, 95%CI 0.44, 2.98, p=0.785). There was no significant difference in the SRS-24 total or domain scores at the end of follow-up between treatment groups ($p>0.159$ for all comparisons). In the whole cohort the bony union did not predict better HRQoL at the end of the treatment (p=0.869), although the pain domain improved significantly in the whole cohort ($p<0.001$).

Conclusion. A rigid thoracolumbar orthosis did not provide any benefits over an elastic lumbar support in terms of bony union or HRQoL outcomes in children with acute spondylolysis.

Trial registration number NCT03675152.

Key words: pediatric spondylolysis; health-related quality of life; Brace treatment

INTRODUCTION

Spondylolysis is the most common cause of low back pain among adolescent athletes, explaining up to 47% of their low back pain [1]. It is a stress fracture by nature, and it is treated with restriction of sports, physical therapy and often using a brace to immobilize the trunk. Previous studies [2-6] have shown good results concerning treatment of adolescent spondylolysis with different kinds of hard orthosis. Boston brace, a rigid thoracolumbar orthosis, is antilordotic to the lumbar spine, which is thought to be favorable for the treatment of adolescent spondylolysis [7]. A biomechanical analysis by Fujimoto et al. 2020 [8] revealed that a custom-made, rigid lumbo-sacral orthosis had the highest restriction in all directions compared to a soft lumbo-sacral orthosis, a custom-molded back cast-panel, a Damen type elasticity corset, and an off-the-shelf soft lumbo-sacral orthosis. However, the natural history of spondylolysis is unclear [9] and there is a lack of prospective comparative studies evaluating the effect of a rigid thoracolumbar orthosis compared to a soft brace on the healing of the defects of the pars interarticularis in pediatric population.

In this study we aimed to examine whether an individualized, custom-made rigid thoracolumbar orthosis (Boston brace) improves the bony union rates of spondylolysis or the health-related quality of life (HRQoL) outcomes when compared to a low-profile, elastic lumbar support (Porostrap) in acute pediatric spondylolysis. We also aimed to figure out factors that affect the bony union of pediatric spondylolysis. We hypothesized that treatment with a rigid thoracolumbar orthosis would improve the bony union rate of the spondylolysis and the HRQoL of patients as compared to treatment with an elastic lumbar support.

METHODS

Trial design

The study was designed as a randomized, non-blinded clinical trial comparing the outcomes of acute pediatric spondylolysis using a Boston brace or an elastic lumbar support. Sample size was calculated with the use of study power of 80% and a type-I error (alpha) of 0.05. The bony union rate of spondylolysis with a Boston brace was assumed to be 90% [3] and with an elastic lumbar support 55% based on our clinical experience. This led to sample size of 22 patients per group and to allow drop outs, a total of 50 patients were included.

The first 14 patients underwent randomization into these two groups (Randomized cohort). An independent observer provided sealed envelopes with the two treatment options and randomization was performed after informing the families about the study and when informed consent was obtained. During this initial enrollment period (June 2016-September 2018) it became quite clear that a large part of the patients and their families refused randomization (22%, 4/18) and wanted to choose the treatment method. To facilitate the recruitment process, the study was modified into a prospective patient preference study (Patient preference cohort, the remaining 36 patients), Figure 1.

Patients

Fifty consecutive children with acute uni- or bilateral spondylolysis were prospectively recruited to this study between June 2016 and October 2020. Inclusion criteria were an acute unilateral or bilateral spondylolysis with bone edema in the spondylolysis in the MRI as a sign of an active lesion, a lesion without bony sclerosis in the CT, and age between 8 and 18 years. Exclusion criteria included spondylolisthesis on a standing spinal radiograph, a systemic skeletal disorder or lack of interest.

Interventions

Patients were treated with a custom-made, rigid thoracolumbar orthosis (individual Boston brace, Respecta, Finland) or a low-profile, elastic lumbar support (Porostrap, Donjoy) for four months.

Additionally, all patients were instructed to avoid physical activities except walking and met a physiotherapist to receive advice on isometric abdominal and spinal muscle exercises.

Radiographic Measures

All patients underwent a standing lumbar radiograph (lateral), a lumbar spine MR images and a selected CT of the fractured vertebra. These images were blindly re-evaluated by an independent musculoskeletal radiologist. From these images spondylolisthesis was excluded, additional stress reactions were noted, and spondylolysis was graded. Grading was done according to Fujii et al. 2004 [10] from the CT images and according to Hollenberg et al. 2002 [11] from the MRI. Bony union was evaluated using a selected CT at four months.

Outcome parameters

The primary outcome parameter in this study was the bony union rate of the spondylolysis with a Boston brace and an elastic lumbar support at four months using CT. Secondary outcome parameters were the HRQoL of the patients before and after the treatment and predictive factors for bony union of the spondylolysis.

HRQoL was measured with the Scoliosis Research Society-24 (SRS-24) outcome questionnaire. It is a questionnaire that Scoliosis Research Society (SRS) originally developed to measure HRQoL of adolescent scoliosis patients but it is widely accepted for use of evaluating HRQoL of other back conditions as well [6, 12, 13]. The questionnaire consists of twenty-four questions and measures seven domains: pain, general self-image, function from back condition, general level of activity, posttreatment self-image, posttreatment function and satisfaction. Every question is scored from one to five and the higher the score the better the outcome. The maximum total score of the questionnaire is therefore 120 points and it is divided by the number of questions resulting into

maximum total score of 5.0. Questions from sixteen to twenty-four concern the treatment and can therefore be filled out only after the treatment.

Statistical analysis

Continuous variables were described as means and standard deviations. Categorical variables were expressed as counts (n) and percentages. Associations between categorical data were analyzed with Fisher's exact test. Comparisons of continuous variables were performed with one-way analysis of variance (ANOVA).

Bony union rates were calculated using log-binomial models. Univariate analysis was performed for the brace type and possible predictive factors for bony union. Only one significant factor was found, and multivariate model was not constructed. Risk ratio for the stage of the spondylolysis in baseline CT was not possible to estimate because all early defects healed. Hence Cochran-Armitage trend test was used to evaluate association between the stage of the spondylolysis in baseline CT and bony union.

Different SRS scores were analyzed with a hierarchical linear mixed model with repeated measures including one within-factor (time), between-factor (group) and the interaction (time*group). Unstructured covariance structure was used for time and Kenward-Roger correction for degrees of freedom was performed. In addition, background characteristics were also examined in order to discover whether they had an effect on the mean change scores between the two measurement points. Univariate analysis was performed for the background characteristics. When only non-significant factors were found, the multivariate model was not constructed.

Posttreatment self-image and function domains of the SRS-24 had skewed distribution and they were analyzed with Mann Whitney U test whereas satisfaction domain was normally distributed and analyzed with ANOVA.

All tests were performed as two-sided with a significance level set at 0.05. The analyses were carried out using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, US).

Ethical committee approval

Ethical committee approval was received from a local Ethics Committee for Human Sciences. A written informed consent from the patient and if needed from his guardians was required. Study was registered to ClinicalTrials.gov (NCT03675152).

RESULTS

Participants

A total of 50 patients participated into this study. One patient was lost to follow-up. Additionally, one patient was excluded, because she had a bilateral pseudoarthrosis with no bone edema in the MRI in the pars interarticularis leaving 48 patients (mean [SD] age at the beginning of the treatment 14.2 years [±1.52 years], 34 males) to be analyzed.

Twenty-eight (58.3 %) patients were treated using the Boston brace and twenty (41.7 %) patients using an elastic lumbar support. The clinical characteristics of the patients are shown in Table 1.

Outcomes

The bony union rates of the spondylolysis (primary outcome) with either a Boston brace or an elastic lumbar support treatment are shown in Table 2. There was no statistical difference in the union rates of spondylolysis treated with a rigid thoracolumbar orthosis or an elastic lumbar support. In 71.4% (20/28) of the Boston brace group and in 75.0% (15/20) of the elastic spinal support group patient had a unilateral defect that healed, or a bilateral defect of which both sides healed (RR 1.14, 95%CI 0.44, 2.98, p=0.785).

In univariate analysis factor that predicted bony union of the spondylolysis (secondary outcome) was the stage of the spondylolysis in baseline CT ($p<0.001$) whereas patient's age, gender, laterality of the spondylolysis, level of the spondylolysis or brace type did not affect bony union ($p=0.785$, all comparisons collected to Table 3).

The HRQoL at baseline did not differ in any domain of the SRS-24 between treatment groups. At the end of the treatment the HRQoL of the patients (secondary outcome) was similar in both treatment groups in all domains of the SRS-24 (Table 4). Total SRS-24 score at 4 months was a mean (95% CI) 3.73 (3.59, 3.86) in patients treated with a Boston brace and a mean (95% CI) 3.85 (3.74, 3.96) in patients treated with an elastic lumbar support (MD 0.128, 95%CI -0.052, 0.308, p=0.159).

The impact of the bony union of the spondylolysis to the HRQoL was evaluated and the results of the SRS-24 scores in patients who did not achieve bony healing of a unilateral defect or both sides of a bilateral defect (non-union group) and in patients who did (union group) are seen in Table 5. The SRS-24 scores at the end of the 4 months treatment in all domains of the questionnaire were at similar level in patients who achieved bony union and who did not (results not shown). When comparing SRS-24 scores before and after the treatment it was noted that pain domain raised in all patients ($p<0.001$) and additionally activity domain raised in patients who achieved bony union of the defect ($p=0.021$) (Table 5).

DISCUSSION

Comparison with existing literature

To our notice, this is a first prospective, comparative study of a rigid thoracolumbar orthosis and an elastic lumbar support for treatment of acute pediatric spondylolysis. Earlier studies have shown good union rates with various kinds of rigid orthosis used for the treatment of adolescent spondylolysis. In our previous study [6] bony union rates with a Boston brace were 82.6% for incomplete fractures and 28.9% for complete fractures. Similar results have been published by other authors as well, where a rigid thoracolumbar orthosis achieves bony union of the spondylolysis for 94% of the early lesions and 37.1-80% of the progressive lesions [3, 4, 5]. Treatment of pediatric spondylolysis with a soft brace is studied mostly with a Damen soft corset, and with it the union rates have been reported to be 62-87-% for the early lesions and 32% for the progressive lesions

[10, 14]. However, there has been a lack of studies comparing braces prospectively with otherwise similar treatment protocols with each other. In this study we could not show any difference in the healing rates when pediatric spondylolysis was treated with a rigid thoracolumbar orthosis or an elastic lumbar support. A low-profile, elastic lumbar support does not give much spinal support and therefore is quite close to the natural history of the spondylolysis. Based on this study a rigid thoracolumbar orthosis is not necessary for treatment of acute pediatric spondylolysis.

When comparing patients HRQoL at the end of the treatment we could not prove that treatment method or achieving a bony union of the spondylolysis would affect it. There is very limited data of the HRQoL of pediatric spondylolysis patients. Zusman et al. 2020 [13] compared adolescent spondylolysis patients' HRQoL with age-matched controls and preoperative adolescent idiopathic scoliosis patients and noticed that spondylolysis patients have lower scores in pain, function and self-image domains of the SRS-22 compared to other two groups. However they measured spondylolysis patients' HRQoL only before possible treatment for spondylolysis. Miller et al. 2004 [15] studied the functional outcome of 40 young athletes with early detected spondylolysis. In their study most of the patients (91%) had an excellent functional outcome based on low back outcome score an average of nine years after the treatment of spondylolysis. Bony union of the spondylolysis was reported in only eleven patients of their cohort.

Strengths and Limitations

There are limitations in this study. Ideally, the effect of a rigid thoracolumbar orthosis on the healing of spondylolysis should be confirmed with a randomized clinical trial. This study was started as a randomized study, but study design was changed after a while due to refuses because of the randomization. Blinding was not possible in the randomized cohort as both treatment options were introduced to the adolescents and their families before informed consent. However, radiologist was blinded to the brace type. Similar problem with randomization was in the BRAIST trial [16]

that compared the effect of a rigid orthosis on the progression risk of adolescent scoliosis. In the BRAIST trial the randomized trial arm was ended before the inclusion requirement was fulfilled because patients wanted to decide themselves between the brace treatment and observation. Patient cohort of 50 patients is considered as sufficient, but a larger study comparing brace treatments would bring more data of this topic.

Another limitation of this study is the follow-up time of four months. It is ideal for evaluating the healing of the spondylolysis but relatively short to evaluate the long-term HRQoL. Sakai et al. 2017 [4] treated adolescent spondylolysis patients with a thoraco-lumbo-sacral-type trunk brace (Sairyo-model hard corset) and followed up patients using monthly MR images after the first presentation and confirmed bony healing with a CT scan. In their study the average time for achieving a bony union of the spondylolysis was 2.5 months for very early lesions, 2.6 months for early lesions and 3.6 months for progressive lesions. Therefore, the treatment time of four months in our study can be considered as sufficient.

In all patients, a selected CT was performed after 4 months' immobilization and this represents the gold standard to define bony union of the spondylolysis. Other strengths of this study include a prospective nature of the study, a standardized treatment protocol and a standardized and validated SRS-24 questionnaire to evaluate the HRQoL.

IMPLICATIONS FOR RESEARCH AND PRACTICE

A rigid thoracolumbar orthosis did not improve the likelihood of achieving bony union for acute pediatric spondylolysis. Therefore, based on this study a rigid thoracolumbar orthosis is not necessary for the conservative treatment of acute pediatric spondylolysis. An even larger, randomized trial comparing the methods of spinal immobilization in treatment of spondylolysis would be needed. A long-term evaluation might reveal, how many of these adolescents will develop

spondylolisthesis during remaining growth. The HRQoL of spondylolysis patients was not dependent of the treatment type or bony union of the pars defect. A long-term, prospective cohort study would bring more information of the HRQoL of pediatric spondylolysis patients.

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Table 1. Characteristics of the study groups

	Boston brace (n=28)	**Elastic lumbar support** (n=20)	**p value**
Age, y	14.4 ± 1.58	13.9 ± 1.41	0.227***
Sex, male %, (No/all)	75 % (21/28)	65 % (13/20)	0.528 **
Duration of symptoms before treatment, y	0.26 ± 0.14	0.24 ± 0.17	0.667***
Treatment time, m	4.25 ± 0.35	4.31 ± 0.45	0.336***
Body mass index	20.5 ± 2.4	21.1 ± 2.6	0.478 ***
Level of spondylolysis			0.721 **
• L5	82% (23/28)	71% (15/21)*	
• L4	18% (5/28)	24% (5/21) *	
• L3	0% (0/28)	5% (1/21)*	
Laterality, unilateral % (No/all)	25% (7/28)	35% (7/20)	0.528 **
Number of fractures in CT	46	33	NA
Stage (CT)			0.308 **
• early	48% (22/46)	24% (8/33)	
• progressive	48% (22/46)	61% (20/33)	
• terminal	4% (2/46)	15% (5/33)	
Number of reactions in MRI	49	35	NA
Stage (MRI)			0.242 **
• stress reaction	16% (8/49)	17% (6/35)	
• incomplete fracture	57% (28/49)	40% (14/35)	
• complete fracture	27% (13/49)	43% (15/35)	
• pseudoarthrosis	0% (0/49)	0% (0/35)	

* one patient had bilateral spondylolysis at L3 and L4 levels, therefore total number of spondylolysis is 21 even though there is 20 patients in the elastic lumbar support group
** **Fisher's exact test**
*** **Analysis of variance (ANOVA)**
NA, not applicable
Values are given as the mean and standard deviation or percentages and counts

Table 2. Bony union rates

Stage of the defect in the pretreatment CT (Fujii et al. 2004)	**Boston brace (number with union / total)**	**Elastic lumbar support (number with union / total)**	**Risk ratio (95% CI)**	**p value**
All defects	71.4% (20/28)	75.0% (15/20)	1.14 (0.44-2.98)	0.785***
Early	100% (13/13)	100% (5/5)	NA**	NA
Progressive	53.8% (7/13)	69.2 % (9/13)		0.688****
Terminal	0% (0/2)	50.0% (1/2) *		1.0****

*one patient had a defect graded as terminal stage in the CT but a complete fracture in the MRI (not pseudoarthrosis) and this defect healed
**risk ratio could not be calculated because all early defects healed
***Log-binomial model
**** Fisher's exact test
NA, not applicable

Table 3. Predictive factors for bony union of pediatric spondylolysis

Factor		**RR**	**95% CI**	**p value**
Brace type				
	Boston Brace	Reference		
	Elastic lumbar support	0.875	0.335, 2.282	0.785**
Gender				
	Female	Reference		
	Male	0.659	0.261, 1.666	0.378**
Laterality				
	Unilateral	Reference		
	Bilateral	1.373	0.443, 4.250	0.583**
Level of spondylolysis				
	Above L5	Reference		
	L5	0.877	0.296, 2.599	0.813**
Stage				
	Early	NA*		<0.001***
	Progressive			
	Terminal			
Age				
	< 14.0 years	Reference		
	≥ 14.0 years	0.833	0.330, 2.106	0.700**

* risk ratio could not be calculated because all early defects healed
** Log-binomial model
***Cochran-Armitage Trend Test

Table 4. SRS-24 outcomes with different brace treatments

SRS domain	Boston brace (baseline n=20, 4 months n=27)	Elastic lumbar support (baseline n=20, 4 months n=19)	Mean difference (95% CI)	p value
Pain				
Baseline	3.42 (3.12, 3.72)	3.54 (3.26, 3.81)	0.11 (-0.28, 0.51)	0.567*
4 months	4.33 (4.12, 4.55)	4.45 (4.23, 4.67)	0.15 (-0.19, 0.43)	0.452*
Self-image				
Baseline	4.27 (3.99, 4.55)	4.52 (4.27, 4.77)	0.21 (-0.13, 0.55)	0.215*
4 months	4.25 (3.99, 4.51)	4.42 (4.04, 4.78)	0.18 (-0.24, 0.59)	0.392*
Function				
Baseline	3.63 (3.34, 3.92)	3.67 (3.43, 3.90)	0.02 (-0.34, 0.37)	0.915*
4 months	3.85 (3.67, 4.04)	3.93 (3.68, 4.18)	0.08 (-0.21, 0.38)	0.567*
Activity				
Baseline	3.96 (3.48, 4.45)	3.95 (3.67, 4.22)	-0.02 (-0.55, 0.52)	0.955*
4 months	4.30 (4.04, 4.56)	4.37 (3.98, 4.76)	0.06 (-0.38, 0.50)	0.785*
Total				
Baseline	3.73 (3.48, 3.97)	3.83 (3.66, 4.00)	0.08 (-0.20, 0.37)	0.556*
4 months	3.73 (3.59, 3.86)	3.85 (3.74, 3.96)	0.13 (-0.05, 0.31)	0.159*
Posttreatment self-image 4 months^	3.00 (3.00, 3.00)	3.00 (3.00, 3.00)	NA	0.224**
Posttreatment function 4 months^	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	NA	0.844**
Satisfaction 4 months	3.70 (3.43, 3.98)	3.84 (3.61, 4.07)	-0.17 (-0.57, 0.24)	0.410***

Values are given as mean and 95% CI
^values are medians and 95% CI
* Hierarchical linear mixed model with repeated measures
**Mann Whitney U test
***Analysis of variance (ANOVA)
NA, not applicable

Table 5. SRS scores before and after the treatment

SRS domain	**Baseline bony union group** (n=29)	**4 months follow-up bony union group** (n=33)	**p value***
Pain	3.39 (3.17, 3.61)	4.38 (4.21, 4.54)	<0.001
Self-image	4.30 (4.09, 4.51)	4.26 (4.00, 4.52)	0.497
Function	3.64 (3.46, 3.83)	3.87 (3.69, 4.04)	0.059
Activity	3.91 (3.58, 4.23)	4.39 (4.16, 4.63)	0.021
Total	3.71 (3.55, 3.87)	3.79 (3.68, 3.90)	0.471
	Baseline non-union group (n=9)	**4 months follow-up non-union group** (n=13)	
Pain	3.76 (3.31, 4.21)	4.40 (4.03, 4.77)	0.011
Self-image	4.70 (4.35, 5.00)	4.49 (4.14, 4.83)	0.218
Function	3.67 (3.14, 4.19)	3.92 (3.64, 4.21)	0.228
Activity	4.11 (3.61, 4.61)	4.15 (3.66, 4.65)	0.903
Total	4.01 (3.70, 4.32)	3.76 (3.59, 3.94)	0.081

Values are given as mean and 95% CI

*Hierarchical linear mixed model with repeated measures

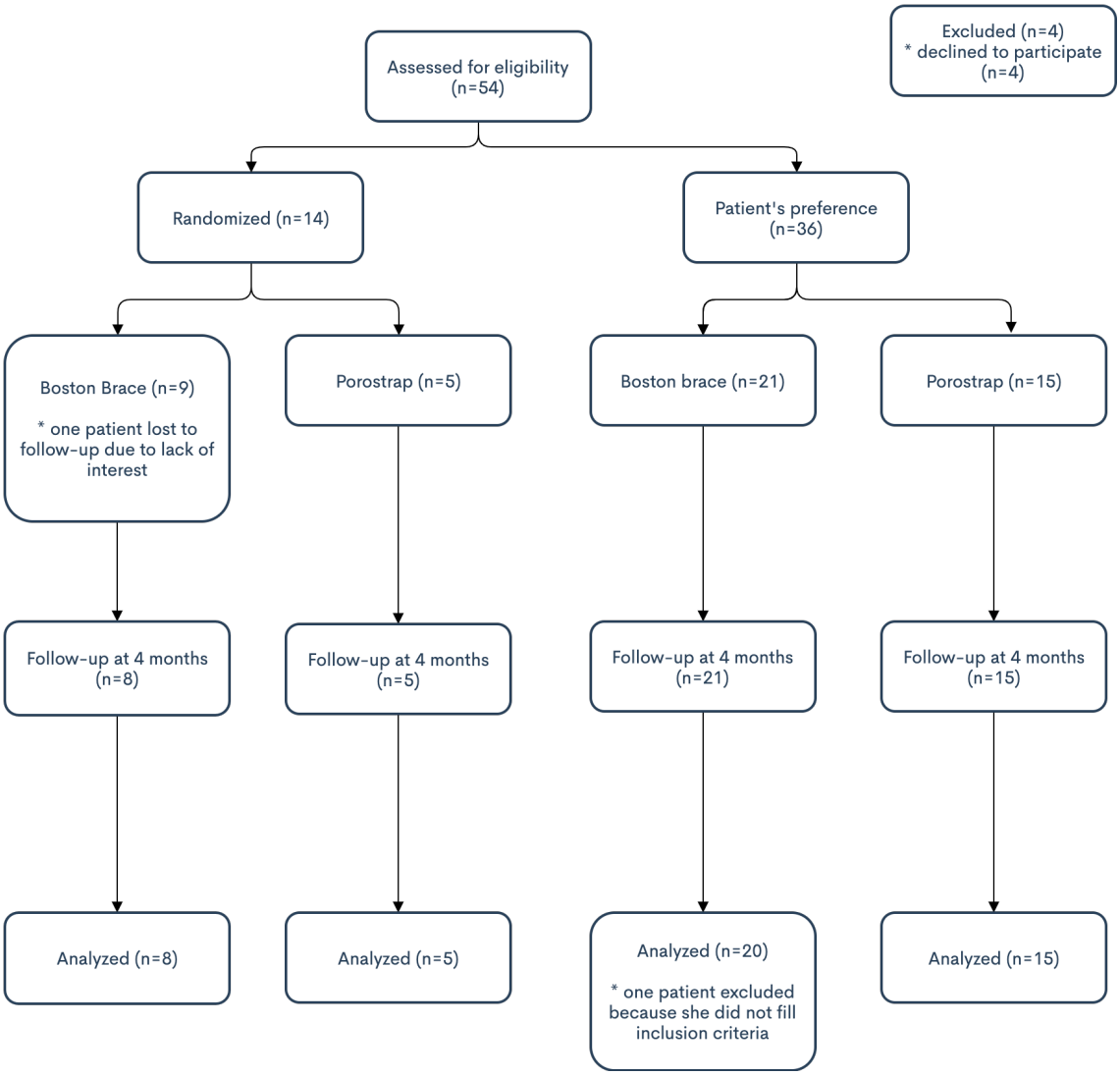

Figure 1. Flowchart

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