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OUTCOME AFTER SURGERY FOR ISTHMIC SPONDYLOLISTHESIS AND DEGENERATIVE DISC DISEASE

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The images on the cover illustrate different types of fusion surgeries. The images have been provided by Peter Endler and Paul Gerdhem.

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Outcome after surgery for isthmic spondylolisthesis and degenerative disc disease

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To my wife and children who allow me to grow and become a better person.

CONTENTS

1 LIST OF ABBREVIATIONS

ALIF	Anterior lumbar interbody fusion
CT	Computer tomography
DRI	Disability Rating Index
EQ-5D	EuroQol-5 Dimension
HRQoL	Health-related quality of life
IBF	Interbody fusion
IPLF	Instrumented posterolateral fusion
MCS	Mental component score
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
ODI	Oswestry disability index
PCS	Physical component score
PLIF	Posterior lumbar interbody fusion
PLF	Posterolateral fusion
SD	Standard deviation
SF-36	Short Form Health survey, 36 items
TLIF	Transforaminal lumbar interbody fusion
VAS	Visual analogue scale

2 ABSTRACT

Individuals with isthmic spondylolisthesis and lumbar degenerative disc disease may have low back and leg pain. Those with persistent symptoms non-responsive to conservative treatment are sometimes treated surgically. Various surgical methods have been introduced, but long-term outcome comparisons are scarce.

The Swedish Spine register (Swespine) was used to study long term outcome after fusion surgery for isthmic spondylolisthesis and lumbar degenerative disc disease. In addition, we determined the effect of loss to follow-up on patient reported outcome interpretation, as well as the diagnostic accuracy of surgical information in Swespine. Another cohort was used to determine the long-term risk of radiologically verified adjacent segment degeneration after interbody fusion and posterolateral fusion.

We found that the Swedish Spine register gives fairly reliable information about the surgical event. Loss to follow-up is of minor importance in the outcome interpretation after lumbar spine surgery. At long term, patient reported outcome was similar when comparing interbody fusion and posterolateral fusion in isthmic spondylolisthesis and degenerative disc disease. The long-term risk of radiologically verified adjacent segment degeneration was similar after interbody fusion and posterolateral fusion. The risk of additional lumbar spine surgery for any reason was significantly higher in those individuals that had undergone interbody fusion compared to those that had undergone posterolateral fusion. Even though patient reported outcome was improved after surgery for isthmic spondylolisthesis, the quality of life did not reach the levels of the normative population.

Key words: isthmic spondylolisthesis, lumbar degenerative disc disease, spine surgery, reoperation, long-term follow-up, Swespine, outcome

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3 SUMMARY IN SWEDISH (SAMMANFATTNING PÅ SVENSKA)

Personer med kotglidning (isthmisk spondylolisthes) och segmentrelaterad smärta (degenerativ disksjukdom) i ländryggen kan ha rygg- och bensmärta. För de med långvariga besvär som inte svarar på konservativ behandling kan operation vara ett behandlingsalternativ. Olika operationsmetoder har introducerats men långtidsuppföljningar och jämförelser mellan olika metoder är få.

Det nationella ryggregistret (Swespine) användes för att studera långtidsutfallet efter steloperation för isthmisk spondylolisthes och degenerativ disksjukdom i ländryggen. Effekten av svarsbortfall av patientenkäter från ryggregistret studerades, liksom hur exakt informationen om kirurgiska ingrepp var i ryggregistret. I en annan grupp undersöktes långtidsrisken för att utveckla tecken på disksänkning på röntgen ovanför stelopererat område i ländryggen.

Vi fann att nationella ryggregistret ger en mycket pålitlig information om det kirurgiska ingreppet. Bortfallet är av mindre betydelse vid tolkning av det långtidsrapporterade utfallet efter ländryggskirurgi. På lång sikt var det patientrapporterade utfallet lika då vi jämförde avancerade med enklare metoder för steloperation. Långtidsrisken för att utveckla disksänkning på röntgen ovanför ett stelopererat område i ryggen var oberoende av operationsmetod. Risken för ytterligare ländryggskirurgi var signifikant högre för de individer som genomgått steloperation som inkluderat kotkropparna jämfört med de som bara genomgått steloperation av de bakre strukturerna i ländryggen. Även om det patientrapporterade utfallet förbättrades efter steloperation av isthmisk spondylolisthes blev aldrig livskvaliteten hos denna grupp samma som hos normalbefolkningen.

4 LIST OF SCIENTIFIC PAPERS

I. **Minor effect of loss to follow-up on outcome interpretation in the Swedish Spine Register**

Peter Endler, Per Ekman, Frida Hellström, Hans Möller, Paul Gerdhem.
Manuscript

II. **Outcomes of Posterolateral Fusion with and without Instrumentation and of Interbody Fusion for Isthmic Spondylolisthesis**

Peter Endler, Per Ekman, Hans Möller, Paul Gerdhem
J Bone Joint Surg Am. 2017;99:743-52

III. **Long term Outcome after Spinal Fusion for Isthmic Spondylolisthesis in Adults**

Peter Endler, Per Ekman, Hanna Ljungqvist, Torkel Brismar, Paul Gerdhem, Hans Möller
The Spine J. 2018 Aug 22 [Epub ahead of print]

IV. **Long term Outcome of Fusion for Degenerative Disc Disease in the Lumbar Spine**

Peter Endler, Per Ekman. Ivan Berglund, Hans Möller, Paul Gerdhem
Manuscript

5 INTRODUCTION

The orthopedic world has evolved tremendously, for example the hip replacement was voted the surgery of the century [1]. The number of implants, different kind of surgeries and indications have dramatically multiplied together with the increasing demands from patients. However, many of the surgeries and implants that have been created have not been thoroughly evaluated to see if they provide any benefit for the patient. The use of implants has increased drastically within spine surgery where lumbar spine fusion surgery is leading the expansion and continues to grow [2].

In Sweden, with a population of slightly more than 10 million inhabitants [3], approximately 12,000 spine surgeries were performed last year [4]. This is still low in comparison to the US [5]. The evidence for the more advanced surgeries and implant use is scarce and heterogenous. We as physicians and profession have a responsibility towards our patients and society to research if what we do actually has any beneficial effect for our patients.

The purpose of this thesis was to increase the knowledge of outcome in lumbar spine fusion surgery for isthmic spondylolisthesis and lumbar degenerative disc disease. An additional purpose was to identify the impact of loss to follow up after spine surgery on outcome interpretation.

6 BACKGROUND

6.1 ISTHMIC SPONDYLOLISTHESIS

6.1.1 Definition

That an anterior subluxation of L5 onto S1 could cause narrowing of the birth canal was described by a Belgian surgeon and obstetrician in 1782. The term spondylolisthesis was first mentioned in 1854 by another obstetrician [6, 7].

Spondylolysis is defined as a defect in the pars interarticularis of the neural arch of the vertebra. The vertebra loses its dorsal fixation and can thereby move forward, which is then called spondylolisthesis [8]. The name spondylolisthesis derived from the Greek words, “spondylos” (meaning vertebra) and “olisthesis” (meaning to slip or slide), includes a heterogeneous group of disorders characterized by the forward displacement of one vertebra on another. Spondylolisthesis is not observed in newborns. The earliest age at

which a pars defect has been reported was in a 3.5 month old infant. The development of spondylolisthesis may be linked to man's ability to stand and the development of lumbar lordosis [9, 10]. It has a high prevalence in athletes [11, 12]. One common theory is that it is a stress fracture of the pars interarticularis of the laminar arch [13]. A genetic predisposition may increase the risk of spondylolisthesis [14]. The incidence of isthmic spondylolisthesis varies with ethnicity, age, and sex. The diagnosis of isthmic spondylolisthesis often occurs around the age of 6 years or in the teenage years [15-19].

The prevalence of spondylolysis is 11.5 % and isthmic spondylolisthesis (slipping of a vertebra) occurs in approximately 4-8% of the population [15, 20-22] and is more common in men than in women (ratio 3:1) [15, 22].

Symptoms vary from none to disabling back pain with or without radiating pain down the legs with restrictions in everyday life. It is most commonly observed in the lowest lumbar vertebrae where 90% occur at L5 and 5% occur at L4 [15, 23]. Spondylolisthesis at more cranial levels is uncommon [24, 25].

6.1.2 **Classification**

The classification developed by Wiltse has become the dominant one when describing spondylolisthesis. [26]. His group divides the spondylolisthesis into five types based on anatomy and etiology They are: Type I, Dysplastic, which is due to dysplasia of the upper sacrum and the facet joints, Type II, Isthmic, which is due to a lesion in the pars interarticularis, Type III, Degenerative, which is due to longstanding intersegmental instability, Type IV, Traumatic, which is due to fractures in other parts of the bony hook than the pars interarticularis, and finally Type V, Pathological, which is due to generalized or localized bone disease [26]. The isthmic type is further subclassified into three groups, type A, due to a lytic fatigue fracture to the pars, type B, elongated, but intact pars and, type C, an acute pars fracture [26]. An additional subgroup is the iatrogenic group where surgery has induced a break in the pars [27].

In 1997, a classification system developed by Marchetti and Bartolozzi [28] distinguished developmental from acquired spondylolisthesis and further divided developmental spondylolisthesis into low and high-dysplastic [28].

Eleven years later, in 2008, Mac-Thiong et al [29] suggested a new classification of spondylolisthesis and divided it into eight groups based on Meyerding grade, degree of

dysplasia, and sagittal balance. The intention was to guide the evaluation and treatment of lumbosacral spondylolisthesis. Tests to validate the system reported high intra-observer agreement but inter-observer agreement was dissatisfying due to the difficulties in distinguishing the level of dysplasia [29].

In 2011, Labelle et al [30] in the Spine Deformity Study Group (SDSG) suggested a classification based on the spino-pelvic posture intended to guide surgical treatment very similar to the earlier classification by Mac-Thiong et al [29], but excluding the dysplasia assessment, giving it six different subtypes to be identified with a substantial intra- and inter-observer agreement [30]. However, further improvements and changes are expected.

6.1.3 **Diagnosis**

Isthmic spondylolisthesis is often found accidentally on radiographs due to the high prevalence of non-symptomatic individuals with the condition [31]. Patients with isthmic spondylolisthesis often have a characteristic step defect when palpating the spinous processes [31]. The step defect is due to the forward slippage of the affected vertebra, bringing the level above with it and leaving the stationary spinous process of the affected level behind. Patients with isthmic spondylolisthesis also have, depending on the severity of the condition, other characteristics like tight hamstrings, altered gait pattern, hyperlordosis and/or pain radiating down one or both legs due to nerve compression [32]. The sign and symptoms of low-grade spondylolisthesis and lumbar degenerative disc disease are very similar in adult patients. This concurs with the knowledge that isthmic spondylolisthesis accelerates degenerative disc disease at the level of slippage [33-35]. Adult isthmic spondylolisthesis can be seen as a disorder associated with low back pain and accelerated disc degeneration [36].

6.1.4 **Imaging**

There are few high-quality studies on imaging in adults with isthmic spondylolisthesis. Evidence based guidelines and gold standard for the diagnosis of isthmic spondylolisthesis is traditional standing radiographs, and possibly with oblique views, even though computer tomography (CT) have become more frequent [32]. In the event of radicular symptoms, MRI is suggested to identify the neuroforaminal stenosis [37-39]. Grading is done on radiographs where the Meyerding classification scale is the most known and used where grade I is 1-25%

anterior translation, grade II is 26-50% anterior translation, grade III is 51-75% anterior translation, grade IV is 76-100% anterior translation and, grade V is over 100% is when the vertebra completely falls off the supporting vertebra (spondyloptosis) [40] Figure 1.

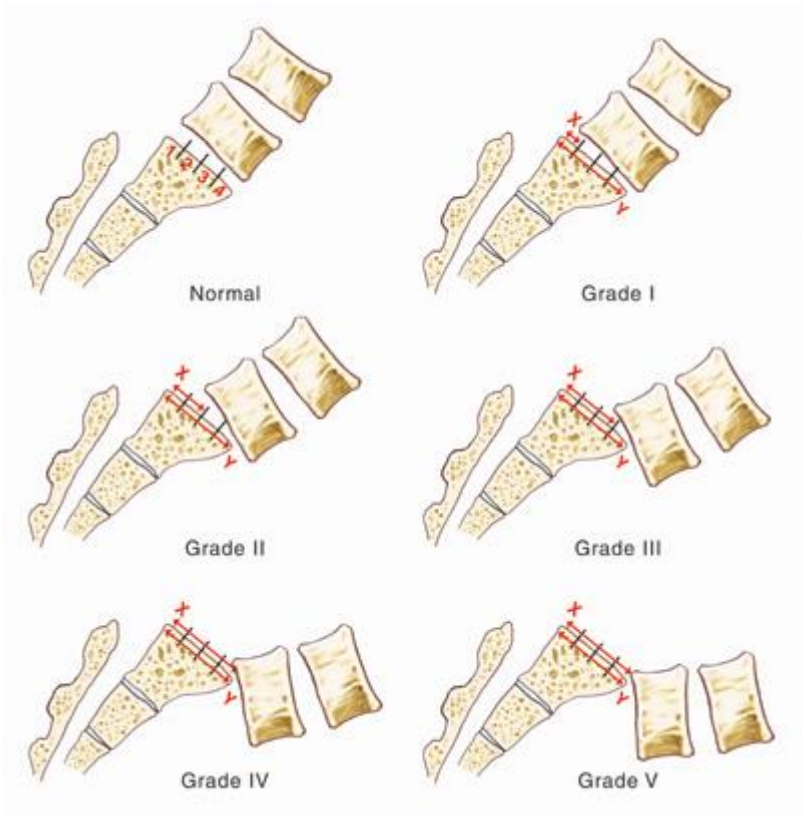

Figure 1. The Meyerding classification of spondylolisthesis I-V. From the smallest (grade I) to the biggest slip (grade V). Figure courtesy of Elsevier Ltd [41].

6.1.5 **Clinical characteristics**

Degenerative disc disease is part of the pathology in isthmic spondylolisthesis. Approximately 50% of all patients with spondylolys (pars defect) develop a vertebral body slipping (listhesis), most often of low-grade (Meyerding 1 and 2) [23].

No definite relationship between isthmic spondylolisthesis and low back pain has been established. In a longitudinal study where children that had been detected with a pars defect in the first year of school and were followed up 45 years later and compared to age matched individuals without the defect, no difference in quality of life was found [15, 20].

In children and adolescents, spondylolisthesis is a fairly common cause of low back pain and radicular pain, however, both of which are more common in adults than in children [31, 42-44].

In severe cases of high-grade isthmic spondylolisthesis, symptoms may include disturbed gait, tightness of the hamstrings, hyperlordosis of the lumbar spine and neurological dysfunction. These symptoms usually appear during adolescence [45]. However, some individuals with high-grade isthmic spondylolisthesis remain asymptomatic [46].

The symptoms and signs in adult patients with low-grade spondylolisthesis are very similar to those patients with chronic low back pain of non-specific origin or caused by degenerative disc disease. This concurs with the knowledge that isthmic spondylolisthesis accelerates degenerative disc disease at the level of slippage [33-35].

6.1.6 **Treatment – conservative**

Most individuals who present with spondylolisthesis are asymptomatic [23]. Nevertheless, symptoms associated with isthmic spondylolisthesis are usually mild and improvement may occur spontaneously. Initial treatment should be conservative and non-operative treatment is successful in the majority of cases. Conservative treatment may include education, non-steroidal medications, selective nerve block injections, brace therapy, restriction of athletic activities and electrical stimulation with transcutaneous electric nerve stimulation [47]. Even though the pars defect does not always heal [48-51], most patients experience improvement of symptoms over time. Studies have shown that the vast majority of adolescents with spondylolysis and spondylolisthesis Meyerding Grade I or II, achieve pain resolution after conservative therapies, with a follow up period of 14 years, leaving 30% for surgical intervention due to pain [52].

Certain studies have reported that using a brace can be beneficial in treating isthmic spondylolisthesis [48, 49, 53]. Positive effects in stabilization training have been observed by O'Sullivan [54]. One randomized controlled study of adults by Möller et al [25], followed up by Ekman et al [24] 9-years later reported less improvement of pain and no effect on functional disability following non-surgical management on isthmic spondylolisthesis.

6.1.7 **Treatment – surgical**

A wide variety of surgical procedures have been described, including techniques for direct repair of the lytic lesion in the pars [54-57]. The rationale for such a procedure is the preservation of motion and was earlier proposed for younger patients with no disc degeneration. However, Schlenzka et al [58] reported that direct repair decreases the mobility of the lumbar spine, does not prevent the disc degeneration and most importantly, leads to worse outcome than that obtained with fusion surgery.

Decompression alone (i.e. Gills procedure) has shown suboptimal results [23, 59, 60]. Reports show that decompression in combination with fusion can increase the risk of pseudoarthrosis in isthmic spondylolisthesis patients and lead to results that are less satisfactory than with fusion alone [61].

Despite the large number of and novel fusion techniques that are available, several studies indicate that the simplest procedure, posterolateral fusion in situ, is just as effective as the more advanced methods, as well as resulting in fewer complications (Paper II) [21, 62-67].

The theoretical advantages that interbody fusion was proposed earlier to have over posterolateral fusion includes, anterior column support, indirect foraminal decompression, lordosis restoration and slippage reduction via ligamentotaxis and removal of part of the pain generating disc [68-71].

Many investigators recommend interbody fusion together with instrumented posterolateral fusion in cases of high-grade slippage (Meyerding grade 3-5) since performance of posterolateral fusion alone may result in a progressive kyphosis [72-74]. Reduction of the slipped vertebra in patients with high-grade spondylolisthesis remains controversial since no clear improvement in outcome has been demonstrated and complications are significantly more frequent [42, 45, 75].

For spondyloptosis (Meyerding 5), vertebrectomy has been reported to result in acceptable outcome despite a high rate of complications [76]. In general, because patients that have high-grade slippage is uncommon and investigations of high quality are lacking, there is at present no general agreement regarding treatment of this group of patients [77].

6.2 DEGENERATIVE DISC DISEASE

6.2.1 **Definition**

A degenerative disc is part of the isthmic spondylolisthesis condition and symptomatology mimics isthmic spondylolisthesis in many ways. Therefore, lumbar degenerative disc disease and isthmic spondylolisthesis are often studied together [78]. Despite its name, degenerative disc disease is not believed to be an acquired disease. Degeneration is linked to the process of aging and has a genetic component [79, 80]. With increasing age, daily stress and minor injuries cause the spinal disc to gradually loose water which makes the rigid outer annulus fibrosus shell weaker [81]. The decreased water content of the intervertebral disc leads to the development of fissures between the nucleus pulposus core and the annulus fibrosus shell. The start of this process, gives rise to altered function of the disc and the beginning of the degenerative destruction of the disc [81]. In a healthy disc, the sensory nerves primarily innervate the outer annulus fibrosus, transferring signals to the adjacent dorsal root ganglion and sympathetic ganglion. In a degenerated disc the innervation is altered, and the nerve endings increase in numbers and protrude as far in as the nucleus pulposus. This enhanced innervation, is thought to be the most important neurological aspect of degenerative disc disease [82]. Genetic and environmental causes like tobacco use have been linked to disc degeneration [81]. These changes of the intervertebral disc will thus affect surrounding structures including the vertebral body and its endplates. The vertebrae will mainly react by sclerosis and osteophyte formation [81]. As the pressure on the intervertebral discs is higher the lower they are situated in the spine, the discs that are affected are usually L4-L5 and L5-S1 [83].

6.2.2 **Classification**

Different classification systems have been proposed where the most common are the Modic classification [84] or the Pfirrmann classification [85, 86]. They differ in the respect that the Modic classification registers changes in the endplate adjacent to the disc and the Pfirrmann classification registers changes in the disc. They both show substantial inter- and intra-observer reliability [87, 88]. The use of invasive diagnostics like discography has been questioned as it has low specificity and its use has been linked to faster progression of the degenerative process [89]. Later classification models have incorporated biomechanical models and considered the lumbar degenerative disc disease as a three-joint complex.

Incorporating the posterior structures in the classifications further drives the classification into trying to predict which candidate is best suited for a specific type of surgery [90]. However further improvements and changes are expected.

6.2.3 **Diagnosis**

The lumbar region is the most common site of disc disease, with the L4/5 and L5/S1 regions being the most commonly affected segments [83]. Setting the diagnosis starts with a thorough pain anamnesis with emphasis on movement correlation. This is followed by deep palpation and flexion of the spine to determine whether the pain can be provoked. When there is absence of another diagnosis and the anamnesis, physical examination and the imaging match the diagnosis, the basis for diagnosis is set [81].

6.2.4 **Imaging**

Both degenerative disc disease and disc changes in isthmic spondylolistheses are classified according to radiographic appearance. Plain radiographs can give clues pointing towards degenerative disc disease such as endplate sclerosis, narrowed disc space, osteophytes and disc vacuum phenomenon (an accumulation of gas, possibly due to osteonecrosis) and listhesis due to the degenerative process [90]. Magnetic Resonance Imaging (MRI) is used to further assess the severity of the degeneration where the density, as well as tears and ruptures of the intervertebral disc, can be examined. The typical radiographic findings in lumbar degenerative disc disease are black discs, disc space narrowing, vacuum disc, end plate sclerosis and osteophyte formation [90]. Nevertheless, individuals with radiological evidence of lumbar disc disease are not necessarily symptomatic.

6.2.5 **Treatment – conservative**

The two cornerstones in conservative treatment of lumbar degenerative disc disease is physiotherapy and pain management. Most often they are performed simultaneously. The focus of the physiotherapy is core-strengthening and back-strengthening exercises [91]. In addition to physiotherapy exercises, patients are encouraged to use their back in daily activities and not be too cautious. Current evidence-based guidelines advocate the endurance of pain to enable physical exercise when it comes to low back pain [92]. Pain management can be divided into a pharmaceutical component and a component of cognitive behavioral therapy (CBT). The medication prescribed first hand is non-steroidal anti-inflammatory drugs since paracetamol has shown equal effect as a placebo for low back pain [93]. The focus of CBT is primarily physical awareness and relaxation exercises [94]. Most cases of degenerative

disc disease can be managed by conservative treatment and does not require surgery for effective pain relief [95-97]. However, cases resistant to conservative treatment may benefit from surgery.

6.2.6 **Treatment – surgical**

In cases of severe, debilitating lumbar degenerative disc disease, surgical treatment is an option and is usually only recommended after at least 6 months of nonsurgical treatment. Which treatment should be preferred for lumbar degenerative disc disease is disputed. Three randomized controlled trials have compared the results of spinal fusion versus conservative treatment [95-97]. Fritzell et al found surgical treatment superior to conservative treatment [95]. This study has been criticized for continuing the same non-effective conservative treatment after randomization [63]. In addition, a long-term follow-up of the same patients could find a difference between the treatment groups in only one variable, being the patients' own experience of how the pain had developed [98]. Brox et al found no difference between conservative and surgical treatment of lumbar degenerative disc disease [96]. This study has, been criticized for being underpowered to identify clinically important differences [92]. The third study by Fairbank et al found a significant improvement difference of disability scores in favor of the surgery group [97]. The authors questioned whether the benefit was superior to the risk of complications with surgery. The current guidelines state that surgical treatment should be considered only after a period of failed conservative treatment or when nonsurgical treatment is unavailable [99].

The decision of which surgery to utilize is currently based on several factors. This includes how extensive surgery the patient can accept and physically tolerate and if the disease pathology is more suitable for a certain type of procedure. In addition, the surgeon's experience and comfort with different procedures weigh heavily in the decision [83]. In a systematic review including 12 randomized controlled trials comparing different types of surgery for lumbar degenerative disc disease, the authors found it difficult to prove any procedure superior to another due to great heterogeneity among the surgical techniques of the studies [100]. It has been reported that instrumentation has higher fusion rates compared to non-instrumented fusion [101]. Successful fusions have been suggested to correlate to fewer reoperations and better clinical outcome. On the other hand, instrumentations are associated with higher surgery costs and a higher risk of complications. The patients who seem to benefit most from instrumentation are those with an increased risk of pseudoarthrosis, including patients who smoke, are unable to wear a brace after surgery, have a kyphotic deformity or a systemic disease associated with poor bone healing [101].

The use of an interbody cage in lumbar degenerative disc disease surgery is suggested to have a higher fusion rate in comparison to instrumented and non-instrumented posterolateral fusion [102]. However, the more invasive surgery is associated with more perioperative complications [102]. Despite the abundance of research on surgery for lumbar degenerative disc disease there is still no consensus on surgery for lumbar degenerative disc disease.

To produce generalizable results regarding any lasting effects of these surgeries, it is desirable with studies with a higher patient number comparing the different kinds of surgeries, assessing reoperation rate and patient-reported outcome measures later than 5 years after operation. Despite several studies comparing the outcome after different types of surgery for degenerative disc disease, there is no consensus reached for the best surgery.

7 THE SWESPINE REGISTER

Swespine, the Swedish spine register, is a national quality registry where patients operated for spinal disorders in Sweden are registered by the treating physician. The aim of the registry is to increase the quality of surgical care of spinal disorders in Sweden. “Coverage” is currently 98% for Swespine; i.e 49/50 clinical departments are registering. Between 75% - 80% of the spine surgeries in Sweden are entered in the registry (“completeness”) [103]. Diagnostic accuracy is 97% (Paper II) [104]. In the year 2017, 9,484 patients who had lumbar spine surgery were entered in the registry [103]. The registry provides questionnaires regarding patient-reported outcome measures that are mailed to patients preoperatively and at 1 (75% follow-up), 2 (67% follow-up), 5 (55% follow-up) and 10 (45% follow-up) years after surgery. The patients complete them without assistance from personnel involved in their care [103]. If the patient has failed to respond to the initial follow-up questionnaires, a reminder is sent by mail. Thereafter, no additional reminders are sent out and non-responders are lost to follow-up.

The type of questionnaires sent out are dependent on the type of spinal disorder that the patient is treated for [103]. As Swespine includes all surgically treated spinal disorders, such as deformities, degenerative diseases in both the lumbar and the cervical spine, as well as infections and metastases, the questionnaires are adapted to assess the outcome in the best way and are area specific [103, 105]. Differences in questionnaire design significantly influence the results of outcome studies [106]. The questionnaires sent out for patient-reported outcome

values are well established and validated, and also recommended by ICHOM (the International Consortium for Health Outcome Measurements) [105, 107, 108].
In the registry 4% are operated for spondylolisthesis, and 7% are operated for degenerative disc disorder [103].

8 OUTCOME MEASURES

8.1.1 Patient reported outcome measures

The EQ-5D, ODI, SF-36, NRS and VAS are patient reported outcome measures that are answered before and after surgery. They offer good validity, reliability and responsiveness for spine surgery [108]. In addition, we used Global assessment and satisfaction which are only answered at follow-up. All measurements reflect how patients perceive their treatment [109, 110]. The EQ-5D is a generic HRQoL (Health-related quality of life) instrument that contains five dimensions of health: mobility, self-care, activities of daily life, pain and depression. Each dimension has three levels. From the instrument 243 different health states can be obtained, and are transformed to a numeric score, (range -0.594-1), lower scores indicating inferior HRQoL [110]. The ODI is a back specific HRQoL instrument that contains 10 items related to limitations in daily life activities (pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and traveling), and is transformed to percentage scored from 0 to 100; higher scores indicate worse symptoms [108, 111]. VAS is a 100 mm scale on which the individual chooses to make a mark. This mark is read with a ruler, with 0 at one end indicating no pain at all and 100 at the other end indicating worst possible pain [109]. NRS which is similar to VAS but is just appreciated from the patient on a scale from 0 to 10 were 10 is worst possible pain [112]. The global assessment of back and leg pain [113] are answered only at the follow-ups. The question on back pain is formulated as follows: “How is your back pain today when compared to before surgery?” and the five answer alternatives are, pain free, much better, somewhat better, unchanged and worsened [113]. The satisfaction question was only answered at the follow-ups and formulated as follows: “Are you satisfied with the surgical result?” and the three answer alternatives were; satisfied, uncertain and dissatisfied.

For Paper III we also used DRI (Disability Rating Index), composed of 12 visual analog scales (VAS), that assess dressing, outdoor walking, climbing stairs, sitting for a longer period of time, standing bent over a sink, carrying a bag, making a bed, running, light work,

heavy work, lifting heavy objects, and participating in exercise/sports. The 12 functional VAS are summed and divided by 12 and provides the DRI, ranging between 0 and 100 [114].

The outcome questionnaires used measure different aspects of health. DRI have been shown to have a high reliability, god compliance and discriminative power between different diagnostic categories with sensibility for small changes [114]. VAS, NRS and DRI reflect perceived levels of pain. Even though the numerical tests cannot be uncritically compared between patients, they can be used to study changes within the same individual and between groups of individuals.

8.1.2 **Additional surgeries**

Data on reoperations (operations on the same segment as the index procedure) and any second index procedure (operations including other lumbar segments) were collected from the time of the index surgery until the long-term follow-up. Reoperation was our primary outcome variable in Paper IV and a secondary outcome variable in Paper II.

8.1.3 **Adjacent segment degeneration**

Fusion of a portion of the spine will increase the mechanical load on adjacent spinal segments and such an effect has been demonstrated in numerous studies [70, 115-124]. Such an increased load might induce or accelerate degenerative changes adjacent to the fusion, as compared to natural history [125]. The frequency of adjacent segment degeneration varies due to the heterogenicity of the criteria for setting the diagnosis [125-129]. Adjacent segment degeneration represents radiographic changes without the symptoms at a spinal level adjacent to a surgically treated level or levels in the spine. Adjacent segment disease is the adjacent segment degeneration but with symptoms. Related symptoms may include radiculopathy, myelopathy, or instability [130]. There is controversy regarding the relationship between degeneration of adjacent segments and its importance in relation to symptoms, where some studies have detected adjacent segment degeneration [130-134] and some that have failed to do so in symptomatic patients [135-140]. The connection between adjacent segment degeneration and symptoms is vague and if this affects the long-term outcome is unclear. Although the accelerated adjacent segment degeneration is occasionally observed, it is not known whether this is the normal aging process or a consequence of the fusion. The extent to

which such a radiological finding reflects a patient's actual symptoms or is just a normal aging of the spine is still uncertain. In spite of this, a wide range of spinal procedures with motion preservation techniques are being developed because of their theoretical superiority in reducing the risk for long-term adjacent segment degeneration. No universal classification system for adjacent segment degeneration currently exists [141]

In Paper III we attempted to bring clarity to the matter. We were able to obtain standard anteroposterior and lateral supine radiographs of the lumbar spine at the time of surgery and at the follow-up. The pretreatment and long-term radiographs were compared, and the degeneration of the first disc above the level of fusion was graded. Two orthopedic spine surgeons with 12 and 26 years of experience and one radiologist with 18 years of experience were available for grading. If no consensus could be reached among the two spine surgeons, the radiologist would determine the grading. We used the UCLA semi-quantitative morphologic grading scale to determine disc degeneration, which, in previous studies, has been shown superior to digital radiographic measurements method and Quantitative Motion Analysis (QMA^{TM}) [125, 128, 142]. Radiographs were classified as normal (grade 1), disc space narrowing (grade 2), presence of osteophytes (grade 3), and end plate sclerosis (grade 4).

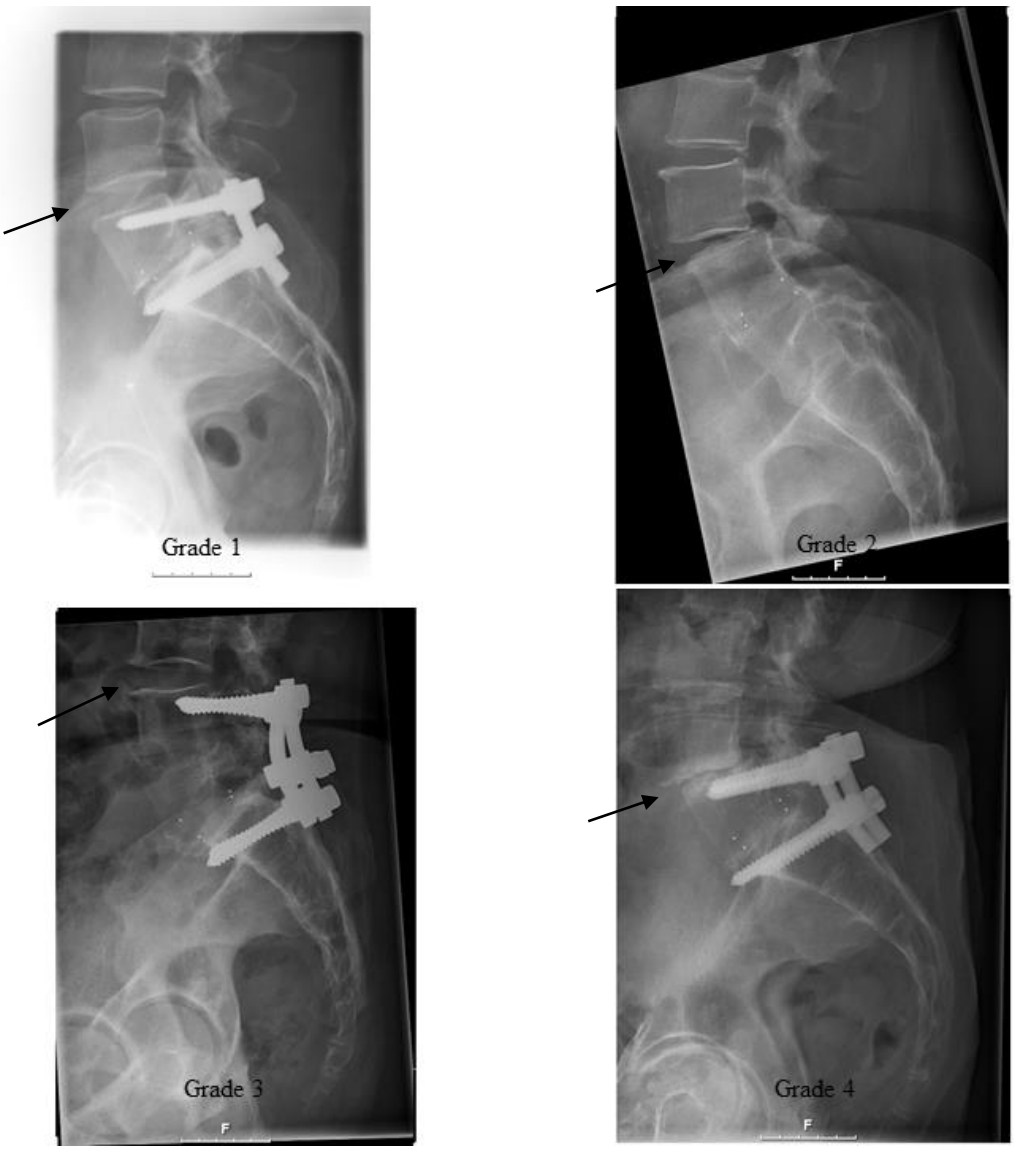

Figure 3. Radiograph illustrating from top left to bottom right, grade 1- 4 in the UCLA grading scale with normal disc (grade 1), narrowing of disc space (grade 2), osteophyte formation (grade 3) and with endplate sclerosis (grade 4). (Radiographs from patients in Paper III).

9 RELEVANCE OF THE CURRENT PROJECT

The central issue is whether lumbar interbody fusion adds something in the surgical treatment of isthmic spondylolisthesis or lumbar degenerative disc disease. The project is of great

significance as there is no consensus on the surgical method that works best. Earlier studies have not been able to provide clarity in the matter. Using a national quality register like Swespine, with a high coverage, increases the generalizability of the results, as they represent the routine surgery performed. The purpose of the thesis was to increase the knowledge of outcome in lumbar spine fusion surgery for isthmic spondylolisthesis and lumbar degenerative disc disease. An additional purpose was to identify the impact of loss to follow-up after spine surgery on outcome interpretation.

10 THE STUDY POPULATION AND METHODS OF APPROACH

10.1.1 **Paper I**

We aimed to evaluate the importance of loss to follow up in the Swedish Spine register, Swespine. Patients operated at Karolinska University hospital or Södersjukhuset for a degenerative lumbar spine disorder and scheduled for a 2 or 5 year postal questionnaire follow up during part of 2016 were identified. From a total cohort of 351 operated individuals, 203 had responded to the first follow-up mail or the first mail reminder from Swespine (i.e the "responders").

To assess the magnitude of the loss to follow up bias, we then approached the 148 individuals that had not responded to the follow-up mails from Swespine (i.e the "non-responders"). After multiple attempts, 115 of the 148 individuals answered to at least part of the follow-up questionnaire. Responders and non-responders patient reported outcome data could then be compared.

10.1.2 **Paper II**

Paper II is a comparison between three different fusion techniques for patients with isthmic spondylolisthesis in Swespine. All patients 18-55 years of age with primary surgery with non-instrumented posterolateral fusion (PLF = 102), instrumented posterolateral fusion (IPLF = 452), or interbody fusion (IBF = 211) due to isthmic spondylolisthesis during a 10-year period were selected. The included patients had to have at least preoperative and two-year follow-up patient reported outcome measurement data. The final study sample consisted of 765 patients with validated surgical data as well as preoperative and 2-year patient-reported outcome data.

Primary outcome was, global assessment of back and leg pain [113]. The secondary outcomes were VAS for back pain and the VAS for leg pain [143], the back-specific Oswestry Disability Index (ODI) [144], the EQ-5D general health questionnaire [145, 146], the mental and physical component summary (MCS and PCS) scores of the Short Form-36 (SF-36) [147-149] up to a mean 6.9 year follow-up, and additional lumbar spine surgeries. Data for additional surgeries consisted of reoperations, i.e. operations on the same segment as the index procedure, and any second index procedure, i.e. operations including other lumbar segments for a mean 10.6-year follow-up.

10.1.3 **Paper III**

This is a long-term follow-up of patients treated surgically for isthmic spondylolisthesis. It is based on (i) a follow-up of a prospective cohort of 86 patients treated with posterior lumbar interbody fusion enrolled between 1997 and 2003 [24], (ii) a historical follow-up of a cohort of 77 patients from a randomized controlled trial treated with posterolateral fusion with or without instrumentation enrolled between 1990 and 1995 and [150], and (iii) 138 controls without known isthmic spondylolisthesis from the general population enrolled between 2014 and 2015.

For the patient cohorts (i) and (ii), the inclusion criteria were the same. At inclusion patients were 18-55 years of age with low back pain, with or without sciatica, with severely restricted functional ability for more than one year, and isthmic spondylolisthesis of all grades and levels. Patients with previous surgery and conditions deemed to affect the capacity to participate in the study were excluded.

The group of patients treated with posterior lumbar interbody fusion were contacted for this study and asked to participate in a long-term follow-up consisting of patient reported outcome measurements questionnaires and radiographs. In the PLIF cohort 73 patients responded to the questionnaires and 77 underwent radiographic examinations. In the PLF group 71 patients responded to the questionnaires and 54 underwent radiographic examinations. The reason for the lower number of x-rays in the PLF cohort is that in 2001, the Swedish radiology storage underwent a digitalization and a lot of x-ray documentation was lost.

Long-term radiological and questionnaire data on the patients treated with posterolateral fusion have been presented earlier [125], but all radiographs were, for this specific study,

reanalyzed, without knowledge of the previous assessment. Radiographs (supine lateral and anteroposterior radiographs) were analyzed using the UCLA semiquantitative method to detect signs of adjacent segment degeneration as described above.

10.1.4 **Paper IV**

In Paper IV Swespine was used to evaluate spinal fusion for lumbar degenerative disc disease. Patients operated during a 15-year period were identified which made it possible to identify a large number of patients with a long follow-up time in combination with as modern surgery as possible. Extraction of data with a minimum of 2-year follow-up time was performed.

All patients 20-65 years of age with primary lumbar spine surgery, operated on with non-instrumented posterolateral fusion (PLF), instrumented posterolateral fusion (IPLF), or interbody fusion (IBF) due to lumbar degenerative disc disease at one or two levels and registered in Swespine were included. The final study sample comprised 2,874 patients with preoperative data and data on additional lumbar spine surgeries.
Primary outcome was additional lumbar spine surgery with a mean follow-up time of 9.2 years. Secondary outcome was patient reported outcome measures up to a mean follow-up of 6.9 years; global assessment back and leg pain, visual analog scale (VAS) for leg and back pain, Oswestry Disability Index (ODI), EuroQol-5 dimensions (EQ-5D), Short Form (SF) 36 and satisfaction of surgery.

11 STATISTICAL ANALYSIS

11.1.1 **Paper I**

In Paper I descriptive data were presented as mean (SD), mean (95% confidence interval), or number (%). Two and 5-year data were analyzed together. In case of missing data, cases were excluded analysis by analysis. The Chi-square test was used for comparison of categorical variables. For group comparisons, logistic regression, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) was utilized. Outcome variables were adjusted for age at surgery (continuous), smoking (yes or no), follow-up time (years), diagnosis (disc herniation, spinal stenosis, other), and if available, the baseline level of the dependent variable**.** Pair-wise comparisons for continuous variables were conducted with Wilcoxon's test. The global assessment questions for both leg and back pain were dichotomized into "pain free" and

"much better" vs. "somewhat better", "unchanged" and "worse". The answer to the satisfaction question was dichotomized into "satisfied" vs. "uncertain" and "dissatisfied". A p-value of < 0.05 was considered significant.

11.1.2 **Paper II and IV.**

Descriptive analysis of patient's characteristics at baseline and follow-up for age, gender, level of fusion, smoking, disability listing, workload, maximum walking distance, pain medication, sick leave and unemployment was performed and presented as mean (SD), mean (95% confidence interval), or number (%). In case of missing data, cases were excluded analysis by analysis. The Chi-square test was used for comparison of categorical variables. For group comparisons, analysis of covariance (ANCOVA) was utilized. Outcome variables were adjusted for statistical differences at baseline and if applicable the baseline value of the dependent variable. Pair-wise comparisons for continuous variables were conducted with Wilcoxon's test. In Paper II and IV the cumulative incidence function and competing risks proportional hazards regression were used with mortality as a competing event to describe the risk of additional surgery. Each patients' underlying cause for reoperation was analyzed and both reoperation and new index surgery was included. Reoperation was defined as a new surgery at the same level as the primary surgery and new index surgery at additional level to the primary surgery. The sensitivity analyses comparing individuals having both 5 and 10-year data was performed in those patients that had data at both time points. A p-value of < 0.05 was considered significant.

11.1.3 **Paper III**

Descriptive data were presented as mean (range), mean (SD), mean (95% confidence interval), or number (%). In case of missing data, cases were excluded analysis by analysis. The Chi-square test was used for comparison of categorical variables. For group comparisons, analysis of covariance (ANCOVA) was utilized. Outcome variables were adjusted for statistical differences at baseline and if applicable the baseline value of the dependent variable. Pair-wise comparisons for longitudinal DRI data were conducted with Wilcoxon's test. The results from the UCLA grading scale of disc degeneration were dichotomized into two groups; normal versus adjacent segment degeneration when comparing the surgical groups. A secondary analysis with patients divided into groups

according to grade of disc degeneration (normal vs adjacent segment degeneration) was performed. A p-value of < 0.05 was considered significant.

12 RESULTS

12.1 PAPER I

Out of the 351 collected patients, 203 (58%) had responded to the first follow-up request or the first reminder sent a month later and were considered responders. The 148 non-responders were contacted and finally, 115 initial non-responders answered, 68 by questionnaire and 47 by mail.

Baseline comparisons between the 203 responders and the 148 initial non-responders showed that the non-responders were significantly younger, more often smokers and were more often treated for disc herniation, while spinal stenosis was more common among the responders. The non-responders had a significantly higher Oswestry disability index (ODI), lower EQ-5D index and SF-36 PCS at baseline. Subgroup analysis at baseline between late responders (´non-responders´) and patients that declined participation or was unable to be reached showed no significant differences (all $p>0.15$).

Analyzing the outcome data, the 203 responders and the 115 non-responders significantly improved from their surgery when compared to base line except for SF-36 PCS in the non-response group ($p=0.063$). According to Global assessment back pain the responders had a higher proportion that were pain free or better compared to the non-responder group ($p=0.002$) and SF-36 MCS was lower in the non-responder group ($p=0.006$) at follow-up. The other patient reported outcome measurements did not differ between the groups ($p>0.06$).

12.2 PAPER II

We validated the surgical data and found excellent conformity (97%) between reported data in Swespine and the original surgical data.

The levels of the fusion were identical in Swespine and the surgical record for 763 of the patients. Swespine reported that 115 patients were registered as having had posterolateral fusion without instrumentation, which could be verified in 101 (88%) of the surgical records. The corresponding findings were 497 and 452 (91%) for posterolateral fusion with

instrumentation and 169 and 151 (89%) for lumbar interbody fusion. Dural tears were listed for 12 patients (2%) in Swespine, and another 17 patients with dural tears were identified in the surgical records. 586 (77%) had longer than 5-year follow-up: 220 patients had 10-year patient-reported outcome data and 366 patients had 5-year data.

A one level fusion was performed in 92% of the patients in the non-instrumented posterolateral fusion group, in 73% of the patients in the instrumented posterolateral fusion group and in 88% of the patients in the interbody fusion group. Decompression was performed in 81% of the patients (56% within PLF, 77% within IPLF and 100% within IBF). All patients in the instrumented posterolateral and the interbody fusion groups were instrumented with pedicle screws. Of the patients in the interbody fusion group, 99% were treated with posterior or transforaminal lumbar interbody fusion.

We adjusted for the baseline differences between the three different fusion groups regarding smoking, fusion level and unemployment and when available the baseline level of the dependent variable for the comparison of the three groups.

All patient reported outcome measurements at baseline were similar with exception for the patient reported outcome data for SF-36MCS who were worse for the non-instrumented group at baseline ($p<0.001$). One year postoperatively the patient reported outcome measures of global assessment back, VAS back pain and satisfaction of surgery were in favor of the instrumented groups compared to the non-instrumented group. This difference was however attenuated at the two-year follow-up with only global assessment back in favor of the instrumented groups and at long-term follow-up (mean 6.9 years) there was no difference between the groups in patient reported outcome measurements.

Additional lumbar spine surgery was either a reoperation, i.e. surgery on the same level as the index surgery, or a new index surgery, i.e. surgery on another level or surgery extending beyond the index level.

The hazard ratio for additional surgery was 4.34 (95% CI 1.71-11.03) for the interbody fusion with regards to the non-instrumented group and the same applied for the instrumented posterolateral fusion group that a hazard ratio of 2.56 (1.02-6.42) for additional surgery compared to the non-instrumented group.

12.3 PAPER III

The three cohorts of 86 posterior lumbar interbody fusion patients, 77 posterolateral fusion patients and the 138 randomly collected individuals from the Swedish population without any known spondylolisthesis, were compared regarding long term patient-reported outcome measurements. The surgically treated groups were also compared regarding the development of adjacent segment degeneration. For all patients, the mean follow-up time of patient-reported outcome was mean (range) 11 (5-16) years and for radiographs 14 (9-19) years.

When adjusted for covariates, both patient groups improved their DRI after surgery with no statistically significant difference between the groups. Both surgical groups scored significantly worse than controls on all parameters with the exception of the SF-36 mental component score which did not differ significantly between the posterior lumbar interbody fusion group and the controls ($p = 0.79$) or the posterolateral fusion group and the controls ($p = 0.12$).

We found that the prevalence of radiological adjacent segment degeneration was 32 out of 77 (42%) patients in the posterior lumbar interbody fusion group and 14 out of 54 (26%) in the posterolateral fusion group ($p=0.98$ after adjustment). In the secondary analysis, which divided the patients according to grade of disc degeneration, 85 normal and 46 with adjacent segment degeneration, adjacent segment degeneration was associated with higher age (52 vs 58 years), but not with patient reported outcomes (DRI, ODI, global outcome, and SF-36MCS and PCS) (all $p \geq 0.24$).

12.4 PAPER IV

Comparing baseline data, the interbody fusion group was younger at surgery. One level fusion and fusion at L5/S1 were dominant in all groups. Unemployment and smoking were more common in the posterolateral fusion group without instrumentation. At baseline, the patient-reported outcomes were similar among the groups, apart from EQ-5D, which was lower (worse) in those to be treated with instrumented posterolateral fusion ($p=0.045$).

At least one additional lumbar spine surgery (new index surgery or reoperation, which ever came first) was recorded for 700 (24%) out of the 2,874 patients and occurred at a mean of 3.1 years after the primary surgery; 424 had a reoperation and 276 had a new index surgery as their first event. In the PLF group, 32 (17%) patients had at least one additional surgery.

Corresponding figures in the IPLF and the IBF groups were 229 (18%) and 439 (31%), respectively. With the PLF group as a reference, the hazard ratio for at least one additional lumbar spine operation was 1.16 (95% CI 0.78 to 1.72) for the IPLF group and 2.13 (1.45 to 3.12) for the IBF group.

Out of the 11 reoperations that followed PLF, seven were due to pseudoarthrosis, two due to infection, and two due to unspecified causes. There were also 21 new index surgeries in this group; eight were due to degenerative disc disease, eight were due to stenosis, and five were due to unspecified causes. Of the 128 reoperations that followed IPLF, 70 were implant-related, 15 due to pseudoarthrosis, seven due to infection, and 36 due to unspecified causes. There were also 101 new index procedures in the IPLF group; 48 were due to degenerative disc disease, 37 were due to stenosis and 16 were due to unspecified causes. Of the 285 reoperations in the IBF group, 179 were implant-related, 50 due to pseudoarthrosis, eight due to infection, and 48 due to unspecified causes. This group had 154 new index procedures; 94 were due to degenerative disc disease, 49 were due to stenosis, and 11 were due to unspecified causes.

The longitudinal patterns of the patient-reported outcomes exhibited a marked improvement from baseline to 1 year and small or no significant changes after 1 year. There were no significant differences in patient-reported outcome among the groups at 1 year, 2 years and long-term follow-up.

13 DISCUSSION

13.1 GENERAL DISCUSSION

Spondylolisthesis is often an incidental radiographic finding on asymptomatic individuals. However, figures as high as 19% has been reported of patients under 26 years of age with low back pain have isthmic spondylolisthesis [151]. This is higher than expected since it is not shown that it is a risk factor to develop low back pain, even though some studies show that spondylolisthesis accelerates disc degeneration of the affected area and this would then be a cause of back pain [33-35]. Thus, even though spondylolisthesis may be asymptomatic it is likely that the defect has an effect on the development of back pain. Despite the common occurrence of sciatica, the usual investigation signs like straight leg raise test and motor and sensory findings are usually negative for both isthmic spondylolisthesis and lumbar degenerative disc disease [152].

Although there have been a relatively large number of studies on the surgical treatment of adult isthmic spondylolisthesis, all were limited by small sample sizes; therefore, the best treatment has not been established [65, 66, 153].

Already 1987 The Quebec Task Force on Spinal Disorders stated that there was lacking scientifically solid evidence of the effect of fusion surgery for low back pain without nerve root compression [154]. More than a decade later a Cochrane review (1999) concluded that there was still no scientific evidence supporting decompression or fusion surgery for degenerative spinal disorders to be more beneficial than the natural history, placebo or conservative treatment [62]. Since then outcome research and the importance of evidence-based medicine has grown.

Despite the growing number of scientific articles produced, there is only one randomized controlled study to date comparing fusion surgery for isthmic spondylolisthesis to conservative treatment [25]. There Möller et al. reported that patients with low back pain with or without radicular pain did better than a group of conservatively treated patients with isthmic spondylolisthesis. There was no difference in the results whether they had radicular pain or not prior surgery, strongly suggesting that there was a mechanical dysfunction involved in their pain. Most previous studies of conservative treatment have included heterogenous groups of patients that included adolescents, young adults and patients with acute onset of pain and spondylolysis where the spondylolysis had the potential of healing [48, 49, 52, 155, 156]. Criticism that has been raised against conservative treatment in randomized controlled trials is the continuation of a failing treatment.

By using the Swedish spine register, Swespine, we have been able to study one of the largest cohorts of patients and one of the longest follow-up times available so far. We believe that the external validity and the internal validity of the register has been strengthened through our studies. In Paper I we were able to show that minor loss of follow-up in the register does not affect the outcome and the interpretation of data from Swespine. In Paper II we reported that the data in the register, which is registered by the treating physician is concordant with the patient files.

This thesis indicates that the use of interbody fusion did not increase the radiological risk of adjacent segment degeneration [157]. Age was more linked to the development of adjacent segment degeneration than the actual fusion technique. However, we cannot exclude that a larger study would have produced another result. Unfortunately, we are unable to determine

whether the increased risk of additional surgery seen in the interbody fusion groups in this thesis (Paper II and IV) is due to an increased risk of adjacent segment degeneration.

13.2 LIMITATIONS AND STRENGTHS

The use of high-quality registers provides certain advantages over randomized controlled studies but also some disadvantages [158, 159]. The main disadvantages are the risk of introducing different kinds of biases that are not always possible to control. Selection bias for the type of treatment chosen by the surgeon is one of them, since we do not know the reasons for the choice of treatment. We suspect that surgeon preference, rather than preoperative symptoms, dictated the use of a specific method. Baseline patient-reported outcomes were similar among the surgical groups. We tried to compensate for known baseline differences by statistical adjustments.

The choice of treatment varied with time. Fusions without instrumentation were done more frequently early on in the study periods and posterolateral fusions with instrumentation and interbody fusions were done more often later in the period, as has also been reported in previous studies [5, 160]. We cannot exclude that the increased risk of additional surgery in the interbody fusion groups is a time effect that surgeons, in general to a larger extent, suggest additional surgery to the patient. For the data on additional surgeries in Paper II and IV we have relied on Swespine data. We do not suspect but cannot exclude a systematic bias; that data on additional surgeries are missing more frequently during early (or late) time periods.

A cost-utility analysis could not be performed because of a lack of data on implant costs and outpatient visits. Therefore, we cannot definitely conclude which fusion technique was the most cost-effective. However, more implants and longer surgery time leads us to suspect higher complication rates and costs for the interbody fusion surgeries when compared to the posterolateral fusion with and without instrumentation [101].

The majority of our patients in the interbody fusion group had surgery either with PLIF or TLIF. Only a handful had undergone standalone ALIF procedures. Separate analyses of the different techniques have not yet been done, so whether different interbody techniques result in different outcomes remain to be investigated.

As with all register studies the question arises whether non-responders will skew the results. Non-response analyses in Paper II and IV indicated that the baseline differences

between responders and non-responders of the questionnaires were very small. In addition, in Paper I, it seemed that loss to follow up has a minor effect on the results, and that even though data differ at baseline between responders and non-responders, patient reported outcome may be similar. We therefore suggest that non-response in Swespine can be treated as a random event.

Whether other aspects, such as imaging differences, could be a reason for treatment choice could not be determined. The Swespine register does not contain information on the grade of slippage or degree of degeneration. However, low-grade slippage is far more common than high-grade slippage in the age group that we studied [36].

The advantage with quality registers is that the inclusion criteria is wide which creates large, heterogeneous sample sizes. Using strict inclusion criteria might, to some extent, lessen the heterogenicity and increase both the internal and external validity. Patient registries are also, due to the greater sample sizes, large enough to detect unusual adverse effects of treatments that might be missed when studying smaller groups, as may be the case with randomized clinical trials.

The major strength of our studies is the size of the cohorts. Other strengths are that we did not rely on register data solely. We validated data in Paper II, and in Paper III we followed up cohorts from two earlier trials to compare the long-term outcome between two different surgical approaches. In Paper I we found that the loss of follow-up in Swespine is of minor importance on the interpretation of outcomes in the long term. We have one of the longest follow-up times described on the subject. We used several well-validated questionnaires that have been recommended for outcome assessment after spinal surgery [108, 161]. Using a national quality register with high coverage increased the generalizability of the results because they represent those of the routine surgery performed.

13.3 TYPE OF FUSION

The wide variety of fusion procedures, including pedicle screw fixation and interbody fusion, offer, at least in theory, advantages over non-instrumented posterolateral fusion. To date no significant difference in the outcomes obtained after the fusion techniques has been proven even though they all claim their superiority [59, 65]. None of the prospective, randomized studies on the long-term effect of treatment of isthmic spondylolisthesis have proven that instrumentation is of benefit in patient-related outcomes [150, 162-165].

At the same time, a slightly higher rate of successful fusion, although without a better clinical outcome, has been reported in connection with instrument-guided fusion [62, 63, 153, 163]. The few randomized controlled trials that exist provide none or only limited evidence that instrumented posterolateral fusion is better than non-instrumented posterolateral fusion [150, 162-165]. Nonetheless, spurred on by new techniques, the frequency of spinal fusions has increased dramatically [160, 166, 167]. However, the evidence in favor of more advanced approaches such as interbody fusion is weak and controversial [166, 168, 169].

There has not been any strong evidence favoring most of the surgical procedures [59, 65]. The theory behind interbody fusion devices is attractive from a biomechanical perspective, because of the anterior column support (where 80% of the axial compression forces are absorbed) [170]. The use of interbody fusion devices has increased and are continuing to increase [2, 5, 160, 167], despite lack of evidence that they are of benefit to the patients. A relatively large number of studies on the subject are available, but all have been hampered by small sample sizes [64, 65, 162-164]. Consequently, the long-term effect of fusion is difficult to assess, and evaluation of surgical treatment without appropriate controls cannot provide evidence for the efficacy of such treatments [166, 171, 172].

Fritzell et al reported that the more demanding techniques are associated with higher risks for the patients and result in longer operation time, more blood transfusions, and more days in hospital after surgery [24, 173, 174]. One Danish study reported that 360^{o} fusion with interbody devices resulted in a better patient reported outcome for individuals treated for degenerative disc disease but not for individuals treated for isthmic spondylolisthesis [78]. Could it be that anterior support is beneficial for the sagittal balance and therefore also the long-term improvement seen in the Danish study? Our results in Paper II, III and IV contradict those results. Our large cohorts also show a higher risk of additional surgery after interbody fusion, irrespective of diagnosis, compared to the less advanced techniques.

13.4 ETHICAL CONSIDERATIONS

In Paper I, II and IV the Swedish Spine register was used. The register uses the opt-out method. Surgical data are entered without consent from the individual. The questionnaire part is voluntary, and the individual is also informed of the possibility to be excluded from all parts of the register. In Paper III patients were specifically asked to participate and could terminate their participation in the study at any time point without consequences.

All papers were approved by the EPN Regional ethical committee in Stockholm (Dnr: 2012/206-31/1 and 2016/1557-32).

13.5 CONCLUSIONS

The major conclusions to be drawn from the investigations described in this thesis are the following. Surgical data and patient reported outcome data in Swespine are rather reliable. In the long term, patient reported outcome of fusion surgery for symptomatic isthmic spondylolisthesis and degenerative disc disease appear to be independent of surgical technique. The plausible advantages of interbody fusion compared to posterolateral fusion could not be verified; no improvement on patient reported or radiological outcome could be demonstrated. Type of fusion surgery does not seem to have any effect of multitude of adjacent segment degeneration between the groups. Interbody fusion seemed to increase the risk of additional lumbar spine surgery.

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16 PAPERS I-IV