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On the Diagnosis and Treatment of Lumbar Spinal Stenosis

KONSTANTINOS PAZARLIS



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Defence on Zoom: <https://uu-se.zoom.us/j/62192626451>

Abstract

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Lumbar spinal stenosis (LSS) is the most common indication for spinal surgery. The aging global population is increasing the demand for strategies that promote physical activity among the elderly. As the prevalence of LSS rises, the condition gains constantly demographic and socioeconomic attention. Until recently, there has been no clear consensus regarding LSS treatment. Further, using electrodiagnostic examinations (EDX) as predictive tools to identify surgical candidates, could lead to a more tailored medical approach. Methodological issues in previous studies have left some questions unanswered. The necessity of extensive surgery for LSS remains a topic of debate among spinal surgeons, which this work addressed by analyzing data from 723 patients.

Parts of the work aimed to compare surgery and structured non-surgical treatment for LSS (Paper I, II, III). Furthermore, it aimed to investigate, by means of EDX, whether the degree of neurological affection correlates to the surgical outcome of LSS (Paper I, II). Additionally, this work evaluated the radiological outcome for surgical vs non-surgical treatment for LSS in terms of sagittal balance parameters (Paper III, V). Finally, parts of this thesis aimed to confirm findings from previous studies regarding DA and DF for LSS with DS (Paper IV, V).

The current thesis is based on two randomized controlled trials and a cohort study: the Uppsala Spinal Stenosis Trial, the Swedish Spinal Stenosis Study, and the Cohort Study on LSS with DS. Patient reported outcome measures from the Swedish National Quality Registry for Spine Surgery (Swespine) were used to collect follow-up data.

We concluded that at six months, surgery with decompression leads to superior clinical outcome, compared to structured physical therapy. The improvement is not affected by delay of surgery (Paper II). EDX does not add predictive value when assessing the patients for eligibility before surgery (Paper II). DA improves the spinal sagittal balance, regardless of preoperative DS (Paper III) and provides good two-year clinical outcome in LSS with DS with low rate of complications, and low need for subsequent surgery (Paper IV). New radiological stenosis was less common two years after DA than after DF, in LSS with or without preoperative DS (Paper V).

Keywords: lumbar spinal stenosis, spine surgery, decompression, fusion, sagittal balance, electrodiagnosis, neurophysiology

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To my Family and my Patients

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Pazarlis, K., Punga, A., Schizas, N., Sandén, B., Michaëlsson, K., Försth, P. (2019) Study protocol for a randomised controlled trial with clinical, neurophysiological, laboratory and radiological outcome for surgical versus non-surgical treatment for lumbar spinal stenosis: the Uppsala Spinal Stenosis Trial (UppSten). *BMJ Open*, 2019;9(8):e030578
- II. Pazarlis, K., Sandberg, A., Lakic, T., Sandén, B., Michaëlsson, K., Punga, A., Försth, P. Clinical and neurophysiological outcome of a Randomized Controlled Trial for the Treatment of Lumbar Spinal Stenosis. The Uppsala Spinal Stenosis Trial (UppSten). *Manuscript*.
- III. Pazarlis, K., Schizas, N., Sandén, B., Michaëlsson, K., Försth, P. Decompression Improves the Sagittal Balance in Patients with Lumbar Spinal Stenosis. A Randomized Controlled Trial: The Uppsala Spinal Stenosis Trial (UppSten). *Submitted (Journal of Neurosurgery: Spine)*.
- IV. Pazarlis, K., Frost, A., Försth, P., (2022) Lumbar Spinal Stenosis with Degenerative Spondylolisthesis Treated with Decompression Alone. A Cohort of 346 Patients at a Large Spine Unit. Clinical Outcome, Complications and Subsequent Surgery. *Spine*, 47(6):470-475
- V. Karlsson, T., Försth, P., Skorpil, M., Pazarlis, K., Öhagen, P., Michaëlsson, K., Sandén, B. (2022) Decompression alone or decompression with fusion for lumbar spinal stenosis: two-year Magnetic Resonance Imaging follow-up. A randomised Clinical Trial. *Bone and Joint Journal* 2022;104 B:1343–51.

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Contents

Introduction.....	11
Diagnosis.....	11
Treatment modalities.....	12
Aims.....	15
Materials and Methods.....	16
The Swedish National Quality Registry for Spine Surgery.....	16
The Uppsala Spinal Stenosis Trial.....	17
The Cohort Study on Lumbar Spinal Stenosis with DS.....	17
The Swedish Spinal Stenosis Study.....	17
Ethics.....	18
Paper I.....	18
Paper II.....	20
Paper III.....	21
Paper IV.....	23
Paper V.....	24
Results.....	26
Paper I-II.....	26
Paper III.....	36
Paper IV.....	40
Paper V.....	42
General discussion.....	46
Cross-over.....	47
Neurophysiology.....	47
Sagittal Balance.....	48
The role of degenerative spondylolisthesis.....	49
Conclusions.....	52
Limitations & Strengths.....	53
Clinical implications and future studies.....	55
Sammanfattning på svenska (summary in Swedish).....	56
Introduktion.....	56
Studie I.....	57

Studie II	57
Studie III.....	58
Studie IV	58
Studie V	58
Slutsatser	59
Περίληψη στα Ελληνικά (summary in Greek).....	60
Εισαγωγή.....	60
Μελέτη I.....	61
Μελέτη II.....	62
Μελέτη III	62
Μελέτη IV	62
Μελέτη V	63
Συμπεράσματα.....	63
Acknowledgements.....	64
References.....	66

Abbreviations

6MWT	6-Minute Walking Test
CI	Confidence Interval
CO	Cross-Over
DA	Decompression Alone
DF	Decompression with Fusion
DS	Degenerative Spondylolisthesis
EDX	Electrodiagnosis
EMG	Electromyography
EQ-5D	EuroQoL Five-Dimensional Questionnaire
FL	Flavum Ligament
FU	Follow-Up
GA	Global Assessment
LL	Lumbar Lordosis
LSS	Lumbar Spinal Stenosis
MRI	Magnetic Resonance Imaging
MUNIX	Motor Unit Number Index
NRS	Numeric Rate Scale
ODI	Oswestry Disability Index
PROM	Patient Reported Outcome Measure
RCT	Randomized Controlled Trial
SSSS	Swedish Spinal Stenosis Study
SVA	Sagittal Vertebral Axis
UppSten	Uppsala Spinal Stenosis Trial

Introduction

The term spinal stenosis is derived from the Greek word “στένωσις” (*sténōsis*), which means narrowing. Evidence of stenosis has been dating back to Ancient Egypt. In modern times, the condition was first described by Antoine Portal in 1803¹. However, it was Verbiest who associated first in 1954 the condition with its clinical symptomatology^{2,3}.

Later, in the 1970's, Kirkaldy-Willis proposed the degenerative cascade model. According to it, the process starts with a dysfunction of a spinal segment (for instance a minor trauma), causing an unstable situation. The spine tries then by thickening the flavum ligaments and producing joint osteophytes, to re-stabilize the segment. These changes, together with the bulging intervertebral discs, lead gradually to narrowing of the canal⁴⁻⁹.

Lumbar spinal stenosis (LSS) is mainly characterized by neurogenic claudication: nonradicular leg and low back pain, gait and balance disturbances, and numbness of the lower limbs^{10,11}. The condition is unusual before the age of 50 and it mainly affects populations aged >65 years. In many countries LSS is the most common indication for spine surgery^{5,10,12-15}. The prevalence of acquired stenosis had been calculated to be more than 7%^{12,16}. The goal of the surgical treatment is to decompress the neural structures in the stenotic segments¹⁷.

Diagnosis

In typical LSS cases, the combination of clinical and radiological examination is often enough to set the diagnosis. The golden standard imaging method is the magnetic resonance imaging (MRI). When the latter cannot be used, for instance in patients carrying older pacemaker models, other alternatives can be used. These include computed tomography (CT) and contrast myelography. Previously, the calculation of the cross-section area on the CT or MRI played a significant role in the diagnosis of LSS. A canal area of 75mm² or less was considered as the cut-off point for stenosis¹⁸. Recently, new research has shown that the absence of cerebrospinal fluid among the spinal roots and their subsequent sedimentation are more representative of spinal stenosis than the

cross-section area itself¹⁹⁻²¹. This evaluation of the spinal canal is made on the T2 sequence of axial MRI. Nowadays, the morphological Schizas classification is widely used.



Figure 1. Spinal stenosis grade C, on T2-weighted axial MRI.

In cases with co-existing neuropathies where the MRI and the clinical examination are insufficient for the differential diagnosis, electrodiagnosis (EDX) plays a very useful role²²⁻²⁴. These EDX modalities include nerve conduction studies and electromyography (EMG). Recent research has shown that EDX could have a predictive value for the treatment of LSS²⁵. EDX is reported to differentiate symptomatic from asymptomatic LSS patients, whereas MRI does not²⁶. The EMG is also helpful in following the progression of the disease. The so-called motor unit number index method (MUNIX)²⁷, a non-invasive and fast surface recording EMG method, has shown good reproducibility in follow-up investigations for cervical spinal stenosis and lumbosacral radiculopathy^{28,29}.

Treatment modalities

The evidence based surgical treatment of LSS is a posterior direct decompression of the stenotic segment. The non-surgical treatment includes a combination of different modalities such as physical therapy (PT), bracing, epidural steroid injections, and other medication³⁰⁻³⁵. After surgery, 60-70% of patients

report satisfaction with the results and a minor proportion of them experience even no improvement at all³⁶. Thus far, there is no consensus regarding the most optimal treatment of LSS. Previous trials have indicated favorable results for surgery whereas others have found good results with non-surgical modalities^{31,37-40}. Moreover, some studies have concluded that surgery's favorable results diminish with time^{41,42}. Apart from that, surgery itself has a positive placebo effect that can improve symptoms in some diseases⁴³. Thus, further research by means of trials with structured non-surgical treatment is needed¹⁰.

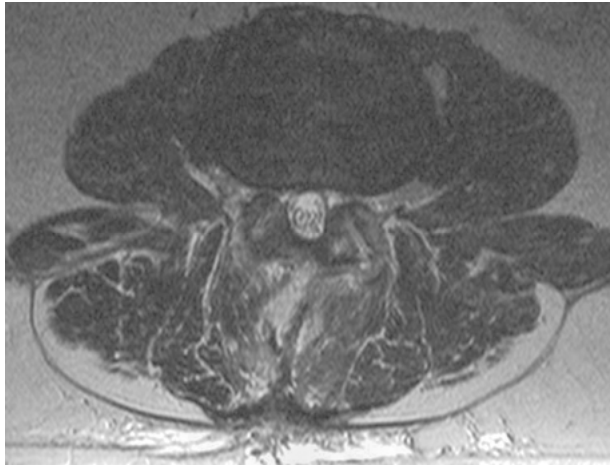


Figure 2. T2-weighted axial MRI showing L3-L4 segment after decompression.

The extension of the lumbar spine decreases the area of the canal. In LSS, this area is already compromised and putting more pressure on the bulging intervertebral discs and the hypertrophic flavum ligament, leads to an increase of the epidural pressure and often to exaggeration of the symptoms. Thus, LSS patients, compensate by leaning forward and decreasing their lumbar lordosis (LL) to relieve the symptoms^{44,45}. As the degeneration of the lumbar spine progresses, the sagittal vertebral axis (SVA) is impaired. The experience gained from previous randomized controlled trials is that the patients' back pain is reduced by decompression alone⁴⁶.

Until recently, it was strongly believed that decompressing a stenotic segment with degenerative spondylolisthesis (DS), would lead to instability and thus a concomitant fusion was necessary. The studies by Herkowitz and Bridwell from the early 90's have been the base for this approach, despite that both

studies included few patients and were not truly randomized^{47,48}. Recent studies have shown that adding fusion for stabilization of a decompressed segment does not provide superior results compared with DA^{46,49,50}. These have been criticized for not evaluating instability by means of flexion/extension radiographies even though this modality has no strong scientific evidence as proper and realistic biomechanical studies are difficult to perform. The use of dynamic plain radiographies does not add value to the evaluation of instability as this method has low accuracy and repeatability and there is lack of consensus on how the examination should be performed^{51,52}. In the same direction, Austevoll et al, found no superiority in adding fusion to decompression in LSS with DS. They have even performed dynamic radiographies where 20% of the patients have been found with a dynamic instability, however without any affection to the outcome⁵³.

The global population is undergoing a rapid aging process, leading to an increasing demand for physical activity solutions among the elderly. The prevalence of LSS also rises with age and has been documented to affect up to 20% of individuals aged 60 to 69¹². This has led to a growing interest in LSS from both demographic and socioeconomic perspectives. Additionally, if it were possible to utilize an EDX examination as a predictive tool for identifying patients who could benefit from surgery, it might enable other patients to avoid surgical interventions and their associated risks. This approach could contribute to a more individualized medical strategy for addressing LSS. Furthermore, previous RCTs have left certain questions unanswered due to methodological concerns such as a high rate of cross-over (CO) and a lack of treatment consistency in non-surgical groups^{35,39}. Finally, the question of whether extensive correction and fusion, in combination with decompression, is necessary has been a debated topic among spinal surgeons. This thesis aimed to address the existing gaps in research and provide solutions to unresolved inquiries by analyzing data from two RCTs and a cohort study.

Aims

The general research questions that this thesis addresses are:

1. Does decompression for LSS lead to superior clinical outcome compared to structured physical therapy?
2. Is there a correlation between the grade of the clinical symptoms and the degree of neurological affection, as measured by EDX?
3. Does decompression for LSS improve the spinal sagittal balance?
4. What are the rates of complications and subsequent surgery after DA for LSS and how frequent is a new stenosis after this procedure?

The specific aims of the individual papers are presented below:

Paper I: to describe the structure of the Uppsala Spinal Stenosis Trial (UppSten).

Paper II: to compare surgical and non-surgical treatment for LSS, and to examine whether the grade of the clinical symptoms correlated with the EDX degree of neurological affection.

Paper III: to compare the radiological outcome for surgical vs non-surgical treatment for LSS, in terms of sagittal balance.

Paper IV: to evaluate the clinical outcome, complications, and subsequent surgery after decompression alone for lumbar spinal stenosis with degenerative spondylolisthesis.

Paper V: to compare the proportion of radiological new stenosis after DA and decompression with fusion (DF), two years post LSS surgery. Further, to evaluate the change in DS two years after DA and DF.

Materials and Methods

The Swedish National Quality Registry for Spine Surgery

Patient reported outcome measures (PROMs) from the Swedish National Quality Registry for Spine Surgery (Swespine) were used^{13,36,54}. The Registry was established back in 1992 with just a few reporting departments in the beginning. Since 1998, Swespine has been in widespread use and today, 25 years later, almost all spine surgery clinics in Sweden refer to the Registry that has achieved a coverage of over 95% with a national follow-up rate of approximately 75%.

The preoperative baseline data are PROM based that the patients enter by themselves and include age, sex, smoking habits, duration of back and/or leg pain before surgery, consumption of analgesics, the Oswestry Disability Index (ODI)⁵⁵, the EuroQoL Five-Dimensional Descriptive system Questionnaire (EQ-5D)⁵⁶, the Numeric Rate Scale (NRS)⁵⁷ for leg and back pain and the subjective walking ability³⁶. Recently, Swespine has been digitalized making its use easier and more comfortable. After the patient is discharged from the hospital, the surgeon registers the peroperative and hospitalization data. This is the only registration that is made by the surgeon. The data include the diagnosis, type of procedure and implants, hospitalization time, antibiotic prophylaxis and complications. Swespine follows-up (FU) the patients at one, two, five and years after surgery. At these points, the patients register the same baseline PROMs accompanied by the global assessment (GA)^{58,59} and the patient satisfaction (PS)¹³. GA represents a useful pain evaluation tool based on a single question: “how is your back/leg pain now compared to before surgery?” The possible answers are: 0-did not have any leg/pain before, 1-completely relieved, 2-much better, 3-somewhat better, 4-not changed and 5-worse.

This thesis is based on the Uppsala Spinal Stenosis Trial (*Paper I-III*), the Cohort Study for lumbar spinal stenosis with degenerative spondylolisthesis (*Paper IV*), and the Swedish Spinal Stenosis Study (SSSS, *Paper V*). Totally,

723 patients with symptomatic lumbar spinal stenosis with and without degenerative spondylolisthesis were included and studied. The detailed patient populations for each Paper are presented further on.

The Uppsala Spinal Stenosis Trial

UppSten is a single-center randomized controlled trial (RCT) with clinical, radiological, neurophysiological, and immunohistochemical follow-up (NCT03495661). All the patients were treated at the Uppsala University Hospital and the inclusion took place from April 2018 to December 2021. The study aimed to compare surgery with decompression and structured physical therapy, for the treatment of LSS. Totally 155 patients were randomized into the two treatments arms: 79 in the surgical and 76 in the PT group. The trial protocol, clinical and neurophysiological outcome, and the radiological results are described in Papers I-III.

The Cohort Study on Lumbar Spinal Stenosis with DS

This work is an observational study based on data from a single high productive spine surgical center. The study included 346 patients with LSS and DS who were treated with DA, without evaluation of any potential instability. Paper IV addresses and presents the clinical outcome, complications, and subsequent surgery of this cohort.

The Swedish Spinal Stenosis Study

The Swedish Spinal Stenosis Study (NCT01994512) was a multicenter, open-label RCT including patients with lumbar spinal stenosis with or without degenerative slip⁴⁶. The participants were randomized into the two treatment arms: decompression alone and decompression with fusion. The research sites were the Uppsala University Hospital, four regional public health hospitals and two private centers for spine surgery in Sweden. All sites participated in the clinical follow-up; one private center did not participate in the radiological FU, which included 222 patients. In Paper V, the two-year radiological results of the study are assessed.

Ethics

The Uppsala Spinal Stenosis Trial was approved by the Regional Ethics Committee (2017-506), the Hospital's Clinical Trials Committee (2018-0001) and the National Biobank Council and Uppsala Biobank (827-2018-025). The Cohort Study was approved by the Regional Ethics Committee (2019-02160). The Swedish Spinal Stenosis Study was approved by the Regional Ethics Committee (2006/196). All the studies were conducted in full compliance with the Helsinki declaration⁶⁰.

Paper I.

Trial design

The Uppsala Spinal Stenosis Trial is an RCT with two treatment arms: surgery with decompression and structural physical therapy⁶¹. The power calculation determined a sample size of 150 patients and was based on ODI which was the primary outcome. An interim analysis was planned when 100 patients would have passed the six-month follow-up to evaluate if an extended inclusion would be necessary to compensate for loss to follow-up. Patients with symptomatic LSS aged 50-85 years were included. A permuted block randomization with variable block sizes was planned through the internet-based randomization software, WebCRF (AKF, Faculty of Medicine and Health Sciences, PO Box 8905 MTF, NO-7491 Trondheim, Norway).

Table 1. Inclusion and exclusion criteria of the trial.

Inclusion criteria

1. Age 50–85 years
2. Clinical symptoms of LSS indicating and motivating surgery. NRS in lower limbs ≥ 3
3. MRI with LSS at 1–3 lumbar levels. Dural sac area ≤ 75 mm² or degree of stenosis C or D according to Schizas classification²⁰
4. The surgical treatment to be provided is decompression alone
5. The patient has given oral and written informed consent to participate

Exclusion criteria

1. Degenerative deformity with Cobb angle $>20^\circ$
2. Spondylolysis
3. Symptomatic osteoarthritis of the lower limbs that affects and limits the patient's function
4. Arterial insufficiency (intermittent claudication)
5. Former lumbar surgery other than disc herniation
6. Conditions that affect the spine, such as ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, spondylodiscitis/infections, malignancy, and neurological diseases
7. Heart and lung diseases presenting a significant risk for surgery or making it impossible for the patient to take part in a physical training program (ASA score >3)
8. Polyneuropathies
9. Psychological factors rendering the patient incapable of inclusion in the trial (e.g. drug addiction, dementia)

Treatment arms

Group A: Surgery with conventional open, facet joint preserving, partial laminectomy under magnification according to the surgeon's own preference (loupes or microscope). Postoperatively the patients were allowed to be mobilized without restrictions, with regular PT instructions and follow-up by a spine physiotherapist.

Group B: Structured PT program on a static bicycle according to a modification of the "Östersund model", which was used in a Swedish observational study on LSS patients (30 min, 3 times/week for 4 months)⁶². The patients in the PT group could at any time cross over to surgery and then receive FU as in group A.

Follow-up

Regular clinical follow-ups at six months, one, two, and five years. Radiological and neurophysiological evaluation at baseline and six months after the allocated treatment was initiated.

Outcome measures

The primary outcome was the ODI which was obtained from Swespine. The secondary outcomes included PROMs from Swespine in terms of the EQ-5D, the NRS for back and leg pain, the subjective walking ability, the global assessment, and the patient satisfaction. Moreover, from EDX, the motor nerve amplitude and the degree of denervation activity were included. The tertiary outcomes were the 6-minute walking test (6MWT)⁶³, the sensory nerve amplitude, F-response latency⁶⁴ and H-reflex⁶⁵, MUNIX, the degree of reinnervation, and finally the LL and SVA. Flavum ligament, which is routinely removed during the decompression, would be collected in the surgical group, and examined with immunohistochemical methods and proteomics analysis regarding inflammation markers and nociceptors. The laboratory part of the UppSten is not included in the current thesis.

Paper II.

The methods used for the clinical part of the project were extensively described above (Paper I).

Electrophysiological methods and examinations

MUNIX, needle EMG and neurography were performed. MUNIX represents an index reflecting the innervation and number of active motor units with good reproducibility^{66,67}. Recording was performed from the anterior tibial (AT) muscle and abductor hallucis (AH) muscle which receive innervation primarily from the L5 and S1 levels. Needle EMG allows to differentiate neurogenic from myogenic disorders in addition to assessing the degree of abnormality. It was performed in muscles innervated mainly from the L4-S1 myotomes to investigate the degree of neurogenic involvement and signs of present denervation. The results from lateral vastus (LV), anterior tibial (AT), and medial gastrocnemius (MG) muscles were shown. The degree of neurogenic involvement was summarized as an “EMG score”, which was calculated for the comprehensive EMG findings of the investigated muscle⁶⁸. In addition to the EMG score, the mean motor unit action potential (MUP) amplitude was measured. The EMG MUP amplitude Z-score (EMG Z-score) was reported to make it possible to pool the results from the three muscles. Signs of ongoing denervation and reinnervation were reported according to Stålberg⁶⁹. Polyneuropathy was diagnosed by means of standard nerve conduction studies and these patients were excluded from the neurophysiological FU⁷⁰.

Statistics - Clinical outcome

The primary outcome, ODI, was analyzed at six months using a linear regression model including its baseline value and the randomized treatment arm. The point estimate of the difference in mean ODI with 95% confidence intervals (CI) and p-value for surgical vs. non-surgical treatment was presented. Continuous outcomes or outcomes that can be assumed as continuous were analyzed according to the primary efficacy analyses. Ordinal outcomes were analyzed using proportional odds regression models including the treatment variable and, if applicable, the baseline value. Odds ratios with 95% CI and p-values were presented for the surgical vs. non-surgical treatment. Exploratory (post hoc) analysis of the Hospital Anxiety and Depression Scale⁷¹ (HADS-A, HADS-D) was performed. SAS version 9.4 (SAS Institute, Cary, USA) and R version 4.2.2 (R Foundation, www.r-project.org) were used in the analyses of the clinical outcome.

Statistics – EDX

The Mann-Whitney U-test was used to compare two groups when a non-normal distribution was assumed in unpaired observations. The Wilcoxon signed-rank test was performed for paired observations. The correlation analysis was performed by means of the Pearson correlation (R) for parametric and the Spearman correlation (Rho) for bivariate non-parametric data. A p-value <0.05 was considered significant. EDX statistical analyses were performed with SPSS Statistics version 28 (IBM Corporation, New York, USA).

Paper III.

All the participants had radiological exams after inclusion and six months after the initiation of the assigned treatment. In cases of cross-over, another radiological evaluation was performed six months after the cross-over surgery. We used full-length standing whole spine radiographs (posteroanterior and lateral), and we calculated the lumbar lordosis, the sagittal vertebral axis and the degenerative spondylolisthesis. The Cobb angle between L1 and S1 was used for the lordosis evaluation and for the SVA, we drew a plumb line from C7 centroid and calculated the distance between that and the posterior superior corner of S1⁷².

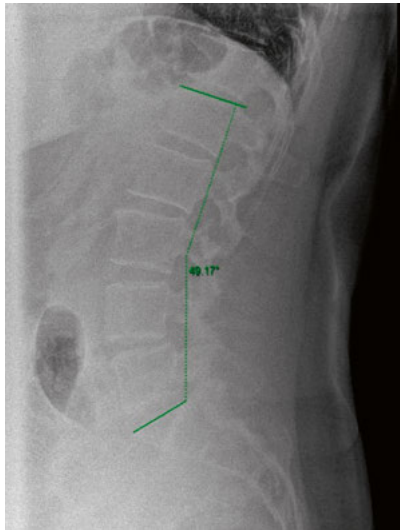


Figure 3. Lumbar lordosis between L1-S1.

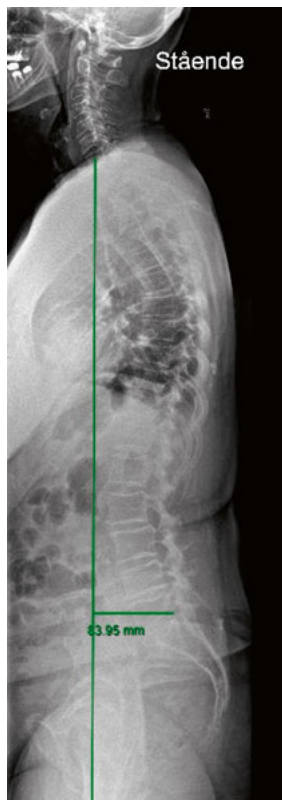


Figure 4. Sagittal vertebral axis.

We included only coronal balanced patients (coronal Cobb angle $<20^\circ$). In accordance with the current evidence, $SVA \leq 50$ mm was considered as the threshold for sagittal balanced spine^{73,74}. We created a DS subgroup to examine the possible effect of preoperative DS on the radiological outcome. DS was defined as a ≥ 3 mm slip of the cranial vertebra related to the caudal one. The evaluation was performed according to Stokes and Frymoyer, without dynamic radiographs⁷⁵.

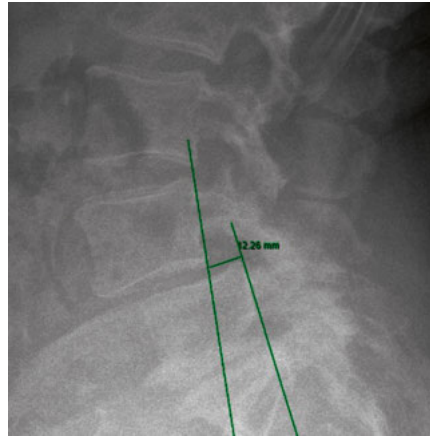


Figure 5. Calculation of degenerative spondylolisthesis L4-L5.

Statistics

The t-test was used for comparison between groups and the paired t-test for the changes from baseline. A p-value of <0.05 was considered as significant and the 95% CI were also calculated. A separate analysis of the CO patients was made. The patients with preoperative DS, were analyzed as a subgroup. The statistical analyses were performed with the use of SPSS Statistics version 28 (IBM Corporation, New York, USA).

Paper IV.

In this project, we studied prospectively collected data from Capio Spine Center Stockholm, which is a high productive spine surgery center. We formed thus a large cohort of patients with a meticulous FU. All the patients had undergone DA without evaluation of any potential instability. PROMs from

Swespine at baseline and two years after surgery were collected and analyzed. Intraoperative and postoperative complications within 30 days of surgery were registered through the local clinic register. All subsequent surgeries in the lumbar spine were registered through Swespine and the local register. The outcome measures used were the ODI, the NRS for low back and leg pain, the EQ-5D and GA.

Statistics

The paired samples t-test was used. P-value of <0.05 considered as significant and the 95% CI were calculated as well.

Paper V.

This project is a follow-up of the multicenter RCT on lumbar spinal stenosis with degenerative spondylolisthesis that was published in 2016 in New England Journal of Medicine⁴⁶. Six centers participated in the two-year MRI follow-up. Stratification for the presence of preoperative degenerative spondylolisthesis on conventional radiographs was performed. The primary outcome was new stenosis at the operated level(s) and/or proximal adjacent level. The secondary outcomes included the stenosis grade according to Schizas (C-D) and absolute dural sac area (mm²). Disc degeneration at the proximal adjacent level was evaluated according to Pfirrmann⁷⁶. The radiological data were assessed by an experienced spine surgeon. The two-year MRI was re-examined for new stenosis by an experienced neuroradiologist. The radiological evaluation was performed on Carestream VuePACS (Carestream Health, USA).

Statistics

The differences between the treatment groups were analyzed by means of the independent samples t-test for continuous variables (Welch's two-sample t-test, independent-samples t-test) and by dichotomized standard summary measures, for ordinal variables (Fisher's exact test, Pearson's chi-squared test with Yates' continuity correction). Analyses were performed both with and without stratification for preoperative degenerative spondylolisthesis. Interobserver reliability between spine surgeon and radiologist was evaluated by using the paired t-test and confidence intervals. Pfirrmann disc degeneration was analyzed as a quantitative variable. The analyses were performed using SAS v.9.4. (SAS Institute, Cary, USA) and R v.3.1 (R Foundation, www.r-project.org).

Table 2. The inclusion and exclusion criteria of the Swedish Spinal Stenosis Study.

Inclusion criteria
Age 50-80 years
Neurogenic claudication, score >30 on visual-analogue scale range from 0-100
1 or 2 adjacent stenotic segments (cross-section area of the dural sac $\leq 75 \text{ mm}^2$) between L2-S1 on MRI
Duration of symptoms > 6 months
Written informed consent
Exclusion criteria
Spondylolysis
Degenerative lumbar scoliosis (Cobb angle >20 degrees)
History of lumbar spinal surgery for spinal stenosis or instability
Stenosis not caused by degenerative changes
Stenosis caused by a herniated disc
Other specific spinal conditions (ankylosing spondylitis, cancer or neurologic disorders)
History of vertebral compression fractures in affected segments
Conditions making participation inappropriate (dementia or drug abuse)

Results

Paper I-II.

Clinical outcome

The screening process identified 409 patients eligible for inclusion. Of those, 63 did not meet all inclusion criteria, and 191 declined participation. Totally, we included and randomized 155 patients; 79 to surgery and 76 to the PT group. During the FU period, ten patients were lost-to-follow-up due to different reasons. At six-month FU, 30 PT patients chose to cross over to the surgical group and received surgery. There were no COs before six months.

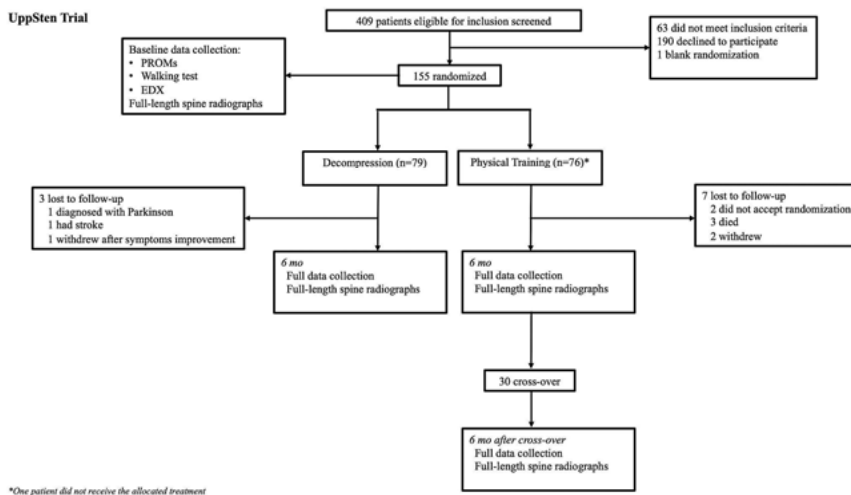


Figure 6. The flow chart of the Uppsala Spinal Stenosis Trial.

Six months after the allocated treatment, there was a clear superiority for the surgical group in all outcomes but for the HADS Anxiety. The mean ODI improvement (*decrease*) in the surgical group was 12.4 units greater than in the PT group. The difference in EQ-5D improvement was 0.16. For the surgical arm compared to the non-surgical one, the odds of improvement in back pain (NRS) were 3.4 times greater, for leg pain (NRS) 8.8 times greater, and 2.9 times greater for the subjective walking ability. In the same direction, surgery had 3.5- and 5.1 times higher odds to improve back and leg pain respectively in terms of GA. The patients who underwent surgery had almost 3.7 times higher odds to be satisfied with the results. The mean improvement in 6MWT was 42 meters greater for the surgical group. Surgery improved HADS-D as well.

Cross-over

Six months after CO surgery, ODI improved compared to its preoperative value (before CO surgery). No improvement was found six months after PT compared to baseline; mean difference -18.7 (95% CI; -25.4; -12.0). The patients who chose CO had worse ODI six months after PT than those who did not choose CO.

Table 3. Baseline characteristics of patients, summarized by the whole study group and for each treatment arm.

Variable	Statistics/Level	Total n=155	Surgical n= 77	Physical Therapy n= 78
Age	n	155	77	78
	Median (Q1 ; Q3)	70.0 (62.0; 75.0)	69.0 (62.0; 74.0)	72.0 (63.0; 76.0)
	Min; Max	(50.0; 82.0)	(50.0; 82.0)	(51.0; 82.0)
<hr/>				
Sex	Male	75 (48.4%)	31 (40.3%)	44 (56.4%)
	Female	80 (51.6%)	46 (59.7%)	34 (43.6%)
<hr/>				
Oswestry Disability Index	n	154	77	77
	Median (Q1 ; Q3)	34.0 (26.0; 44.0)	36.0 (26.0; 48.0)	32.0 (26.0; 42.0)
	Min; Max	(6.0; 70.0)	(6.0; 68.0)	(8.0; 70.0)
<hr/>				
EQ-5D	n	154	77	77
	Median (Q1 ; Q3)	0.66 (0.16; 0.73)	0.66 (0.16; 0.73)	0.66 (0.16; 0.73)
	Min; Max	(-0.07; 0.88)	(-0.07; 0.80)	(-0.02; 0.88)

Variable	Statistics/Level	Total n=155	Surgical n= 77	Physical Therapy n= 78
Back pain (NRS)	n	154	77	77
	Median (Q1; Q3)	6.0 (4.0; 7.0)	6.0 (4.0; 8.0)	6.0 (4.0; 7.0)
	Min; Max	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)
Leg pain (NRS)	n	154	77	77
	Median (Q1; Q3)	7.0 (5.0; 8.0)	7.0 (5.0; 8.0)	7.0 (4.0; 8.0)
	Min; Max	(0.0; 10.0)	(1.0; 10.0)	(0.0; 10.0)
Subjective walking ability	n missing	1		1
	<100m	37 (24.0%)	16 (20.8%)	21 (27.3%)
	100-500m	45 (29.2%)	21 (27.3%)	24 (31.2%)
	500-1000m	25 (16.2%)	15 (19.5%)	10 (13.0%)
	>1000m	47 (30.5%)	25 (32.5%)	22 (28.6%)

Variable	Statistics/Level	Total n=155	Surgical n= 77	Physical Therapy n= 78
6MWT (m)	n	150	76	74
	Mean (SD)	337.7 (114.3)	318.3 (106.8)	357.5 (119.1)
	Median (Q1; Q3)	350.0 (262.0; 422.0)	333.5 (237.0; 400.0)	377.5 (273.0; 445.0)
	Min; Max	(0.0; 585.0)	(50.0; 512.0)	(0.0; 585.0)
HADS Anxiety	n	152	77	75
	Median (Q1; Q3)	4.0 (1.0; 7.0)	4.0 (2.0; 7.0)	4.0 (1.0; 7.0)
	Min; Max	(0.0; 16.0)	(0.0; 16.0)	(0.0; 14.0)
HADS Depression	n	152	77	75
	Median (Q1; Q3)	3.0 (2.0; 6.0)	3.0 (2.0; 6.0)	3.0 (2.0; 6.0)
	Min; Max	(0.0; 15.0)	(0.0; 15.0)	(0.0; 14.0)

Table 4. The effect of treatment on outcomes at six-month follow-up visit.

	Outcome	N	Treatment effect estimate (95% CI) Surgery vs Physical Therapy	p-value
Primary outcome	Oswestry Disability Index	144	-12.4 (-17.0; -7.86) ^a	<0.0001
Secondary outcomes	EQ-5D	144	0.16 (0.08; 0.24) ^a	0.0002
	Back pain (NRS)	144	3.42 (1.88; 6.25) ^b	<0.0001
	Leg pain (NRS)	144	8.82 (4.56; 17.05) ^b	<0.0001
	Subjective walking ability	144	2.88 (1.50; 5.55) ^b	0.0015
	GA Back pain ^c	135	3.53 (1.87; 6.65) ^b	<0.0001
	GA Leg pain ^c	139	5.12 (2.68; 9.78) ^b	<0.0001
	Patient satisfaction	144	3.66 (1.91; 7.00) ^b	<0.0001
Tertiary outcomes	6MWT (m)	143	42.22 (18.08; 66.35) ^a	0.0007
Exploratory analyses	HADS Anxiety	143	1.34 (0.75; 2.40) ^b	0.3227
	HADS Depression	143	2.67 (1.45; 4.91) ^b	0.0016

^a Treatment effect estimate from linear regression model, presented as difference (with 95% CI) in model adjusted means.

^b Treatment effect estimate from proportional odds regression model, presented as odds ratio for having better results (i.e. having higher values for the variable "Subjective walking ability" and lower values for the other ordinal outcomes).

^c The subjects with value 0 for GA Back pain and GA Leg pain variables were excluded.

All models except for the GA and PS outcomes, included baseline results in addition to the randomized treatment.

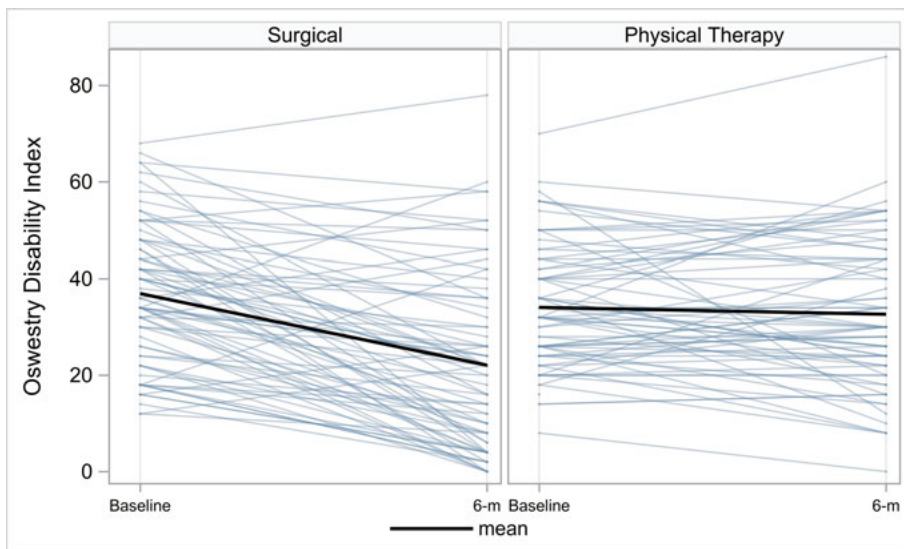


Figure 7. Improvement in ODI at six months.

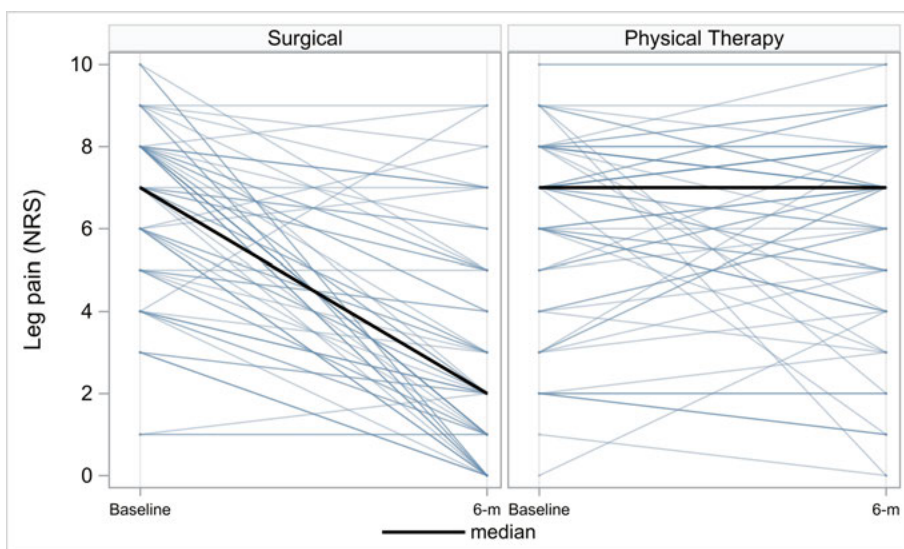


Figure 8. Improvement in leg pain (NRS) at six months.

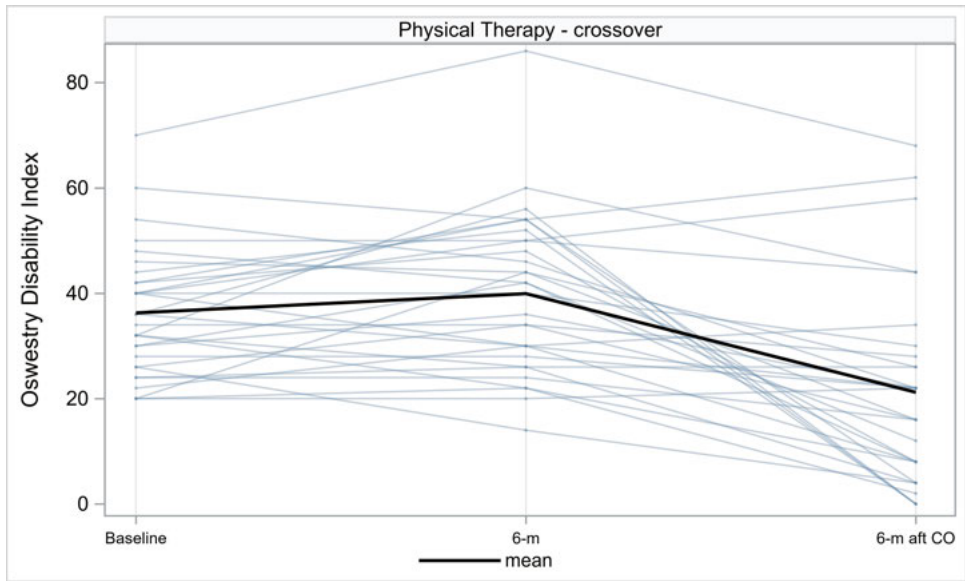


Figure 9. ODI improvement after CO surgery.

EDX outcome

The neurophysiological analysis included 134 patients, 67 from the surgical; and another 67 from the PT group. The degree of neurogenic involvement measured by EDX was modest, and the large spread of data made overall interpretations difficult. We found that the degree of peripheral motor neuron involvement and the presence of active denervation at baseline related to short walking distance (6MWT). Nevertheless, there were no correlations after the interventions. Tables 5 and 6 present the EDX results in detail.

Table 5. Correlations between the baseline clinical parameters, active denervation, and the baseline EDX parameters for all the participants before interventions.

Correlations Baseline	Baseline	Correlation coefficient	P-value
ODI	MUNIX (relative)	0.014 (R)	0.78
ODI	CMAP (relative)	-0.02 (R)	0.69
ODI	EMG score	-0.004 (Rho)	0.90
ODI	EMG MUP ampl Z score	-0.068 (R)	0.069
ODI	EMG active denervation	0.027(Rho)	0.46
Pain, back			
Pain, back	MUNIX (relative)	0.062 (Rho)	0.22
Pain, leg	MUNIX (relative)	-0.02 (Rho)	0.69
Pain, back	CMAP (relative)	0.03 (Rho)	0.56
Pain, leg	CMAP (relative)	-0.037 (Rho)	0.47
Pain, back	EMG score	-0.052 (Rho)	0.16
Pain, back	EMG MUP ampl Z score	-0.056 (Rho)	0.13
Pain, back	EMG active denervation	-0.031 (Rho)	0.40
Pain, leg	EMG score	-0.14 (Rho)	<0.001
Pain, leg	EMG MUP ampl Z score	-0.17 (Rho)	<0.001
Pain, leg	EMG active denervation	-0.003 (Rho)	0.94
6MWT			
6MWT	MUNIX (relative)	0.15 (R)	0.003
6MWT	CMAP (relative)	0.18 (R)	<0.001
6MWT	EMG score	-0.11 (Rho)	0.003
6MWT	EMG MUP ampl Z score	0.006 (R)	0.86
6MWT	EMG active denervation	-0.13 (Rho)	<0.001
EMG active denervation			
EMG active denervation	MUNIX (relative)	-0.29 (Rho)	<0.001
EMG active denervation	CMAP (relative)	-0.26 (Rho)	<0.001
EMG active denervation	EMG score	0.47 (Rho)	<0.001
EMG active denervation	EMG MUP ampl Z score	0.28 (Rho)	<0.001

Table 6. Mean values for the EDX parameters before and after interventions.

	Before surgery	After surgery	P-value	Before PT	After PT	P-value
MUNIX (% abnormal)	7.5	12	p=0.033	10	14	p=0.24
MUNIX (relative, mean)	0.83	0.82	p=0.41	0.80	0.75	p=0.20
CMAP (% abnormal)	9.0	12	p=0.13	14	18	0.072
CMAP (relative, mean)	0.94	0.90	p=0.015	0.91	0.86	p=0.004
EMG (score, mean)	0.45	0.52	p=0.018	0.52	0.60	p=0.052
EMG (% abnormal)	31	35	p=0.055	36	40	p=0.13
EMG MUP Z (score, mean)	1.5	1.6	p=0.29	1.6	1.8	p=0.031
Active denervation (%)	7.7	7.5	p=0.84	11	11	p=0.85

Complications, reoperations, and Serious Adverse Events (SAEs)

In the surgical group, one patient had an epidural bleeding that led to prolonged hospitalization, and six patients had an accidental durotomy (AD). Of those six patients, one had also a postoperative haematoma that needed surgical treatment, however without residual symptoms. Two more patients had revision surgery due to haematoma, in one case complicated by residual drop foot. In the same group, within one week postoperatively, four patients had a superficial surgical site infection. In one case, this led to a deep infection (later than one week postoperatively) which was treated by surgical debridement. Other complications included two patients with severe pain, one with prolonged hospitalization/rehabilitation, one urinary retention, two urinary tract infections (UTI) and one medicine related complication. There were no thromboembolic or cardiac complications. Four SAEs were identified; osteosynthesis for hand fracture, surgery for metastatic cancer (non-spinal), hip surgery and stroke.

In the CO subgroup, there were two ADs, whereas two other patients had a postoperative haematoma but without need for surgical evacuation and without residual symptoms. There were no thromboembolic or cardiac complications and no reoperations in this subgroup. One SAE in terms of UTI that needed hospitalization was registered.

There were no physical therapy related complications. The SAEs in the PT group included surgery for kidney stone, stroke, revision surgery for hip implant failure and surgery for upper extremity fracture. In one patient pneumonia led to sepsis and death.

Paper III.

Six months after the allocated treatment, the surgical group had higher mean LL (49.4° vs 43.0° ; 95% CI, 2.4 to 10.5) and a tendency towards better mean SVA, than the PT group (39.4 vs 51.2 mm; 95% CI, -24.6 to 1.1). In the surgical group there was an improvement from baseline for LL (mean difference 3.2° ; 95% CI 1.5 to 4.9) and a tendency towards improvement in SVA (mean difference -6.5 mm; 95% CI, -13.9 to 1.0). In the PT group, there was no difference regarding LL (mean difference -0.9° ; 95% CI, -2.7 to 1.0) and SVA (mean difference 5.7 mm; 95% CI, -2.5 to 13.9).

DS subgroup

Sixty patients with preoperative DS were identified: 33 in the surgical and 27 in the PT arm. We found an improvement for LL in the surgical group and an increase of the DS in the PT group. There were only two patients without preoperative DS, one from each group, who were found to have DS after intervention.

Table 7. Baseline data.

	All patients			DS subgroup	
	Decompression (n=79)	Physical Therapy (n=76)	Decompression (n=33)	Physical Therapy (n=27)	Physical Therapy (n=27)
Age (years)	68.4 ± 8.0	69.2 ± 8.0	69.3 ± 8.6	68.7 ± 8.8	68.7 ± 8.8
Sex (m/f %)	40/60	57/43	30/70	40/60	40/60
1-Level (%)	57	58	76	59	59
2-Level (%)	33	33	15	37	37
3-Level (%)	10	9	9	4	4
LL (°)	45.9 ± 13.2	43.7 ± 10.4	46.9 ± 14.8	47.1 ± 10.4	47.1 ± 10.4
SVA (mm)	45.9 ± 45.3	43.4 ± 40.0	58.7 ± 44.7	50.2 ± 41.8	50.2 ± 41.8

Table 8. Six-month radiological outcome.

Six-month Radiological Outcome						
All patients			DS subgroup			
	Decompression (n=73)	Physical Therapy (n=71)	P-value	Decompression (n=32)	Physical Therapy (n=27)	P-value
LL (°)	49.4 ± 13.5	42.9 ± 11.0	0.002	50.9 ± 14.0	45.4 ± 12.3	0.12
SVA (mm)	39.4 ± 38.3	51.2 ± 39.6	0.07	44.9 ± 37.7	53.8 ± 43.8	0.41
DS (mm)				5.9 ± 2.6	5.7 ± 1.5	0.77
Difference from Baseline						
All patients			DS subgroup			
	Decompression (n=73)	Physical Therapy (n=70)	P-value	Decompression (n=41)	Physical Therapy (n=43)	P-value
LL (°)	3.2 ± 7.2	-0.9 ± 7.6	<0.001	3.8 ± 7.9	-1.7 ± 9.2	0.36
SVA (mm)	-6.5 ± 32.1	5.7 ± 34.5	0.09	-11.3 ± 34.3	3.6 ± 36.8	0.62
DS (mm)				0.00 ± 1.5	0.5 ± 1.1	0.03

Cross-Over

Thirty patients from the non-surgical arm chose to cross-over to surgery, six-month after their treatment, 63% male and 37% female. The mean age of the subgroup was 68 years old (SD ± 9), whereas 63% had one-level, 27% two-level and 10% had three-level LSS. The preoperative data of the CO subgroup are presented in Table 9. Six months after surgery, the CO subgroup had *less LL*, compared to the patients who were randomized to surgery (42.4° vs 49.4° ; 95% CI, 1.1 to 12.7). There was no difference regarding SVA (46.7 vs 39.4 ; 95% CI, -23.3 to 7.6). We found a tendency towards worsening of both LL (mean difference -1.4° ; 95% CI, -3.5 to 0.8) and SVA (mean difference 7.6 ; 95% CI, -1.3 to 16.4) compared to the inclusion baseline. Moreover, CO surgery *did not improve* the LL and SVA that these patients had before CO (LL mean difference 0.6° ; 95% CI, -2.4 to 3.7 and SVA mean difference -6.2 mm, 95% CI, -17.4 to 4.9).

Table 9. The upper part of the table presents the six-month results of the CO subgroup, compared to the six-month results of the patients who were originally randomized to surgery. The lower part compares the six-month results of the CO subgroup to their inclusion and to their values before CO surgery.

Cross-Over				
	Randomized to Decompression (n=73)		Cross-Over to Decompression (n=30)	P-value
LL (°)	49.4 \pm 13		42.4 \pm 13	0.02
SVA (mm)	39.4 \pm 38		46.7 \pm 32	0.4
	Difference from Inclusion Baseline		Difference before/after cross-over surgery	
		P-value		P-value
LL (°)	-1.4 \pm 6	0.2	0.6 \pm 8	0.7
SVA (mm)	7.6 \pm 23	0.09	-6.2 \pm 29	0.3

Paper IV.

Two years after surgery, there was an *improvement* in all PROMs (ODI, NRS for back and leg pain and EQ-5D). The GA success rate for back and leg pain was 68.3% and 67.6% respectively. Success rate was defined as the proportion of patients who reported complete recovery or much improved⁵⁹.

Forty-one patients had at least one intra- or postoperative *complication* within 30 days from surgery (11.9%). These included 17 superficial wound infections (4.9%), 12 accidental dural tears (3.5%), eight urinary tract infections (2.3%) and four cardiovascular events (1.2%). Two patients had a deep wound infection (0.6%) whereas pneumonia and sepsis were found in one patient respectively (0.3%). Four out of the 41 patients had two complications.

Nine patients (2.6%) underwent *subsequent surgery* within two years of the primary surgery. During the whole period of data collection, i.e., as of June 2020, 28 patients had undergone subsequent surgery (8.1%) whereas eight of them had had two surgeries. Table 11 describes the subsequent surgery in detail.

Table 10. Clinical outcome.

	Baseline mean	2-year FU mean	Mean difference	95% CI of the Difference		p-value
				Lower	Upper	
ODI	36 ± 15	20 ± 18	16 ± 17	14	18	<0.05
NRS back	5.5 ± 2.7	2.8 ± 2.7	2.7 ± 3.1	2.3	3	<0.05
NRS leg	6.4 ± 2.6	2.7 ± 2.9	3.7 ± 3.5	3.3	4	<0.05
EQ-5D	0.46 ± 0.30	0.70 ± 0.29	-0.24 ± 0.34	-0.28	-0.20	<0.05

Table 11. Subsequent surgery.

Subsequent Surgery among 346 patients			
Localization of subsequent surgery	Subsequent Surgery within 2 years	Subsequent Surgery 1 total	Subsequent Surgery 2 total
Same level(s)	5	17	2
Same level(s) + new	2	6	4
Purely new level(s)	2	5	2
Mean time to surgery - days (range)	369 (105-644)	937 (105-2513)	1778 (1010-2831)
Male	4	8	3
Female	5	20	5
Total	9 (2.6%)	28 (8.1%)	8 (2.3%)
Diagnosis for subsequent surgery	Subsequent Surgery within 2 years	Subsequent Surgery 1 total	Subsequent Surgery 2 total
Lumbar Disc Herniation	3	3	0
Degenerative Disc Disease	1	9	3
New Level Stenosis	1	6	2
Residual Stenosis	1	3	0
Recidivate Stenosis	4	8	2
Postoperative Haematoma	0	0	1

Paper V.

A total of 222 patients were enrolled. The inclusion took place between September 2006 and February 2012. Of those, 211 patients received the assigned treatment; 103 underwent DF and 108 had DA. Two years after surgery, LSS *at the operated and/or proximal adjacent level* was more common after decompression with fusion (47%) than after decompression alone (29%; $p=0.02$). The difference remained significant in the DS subgroup, (48% vs 24%; $p=0.02$), but not in absence of DS (45% vs 35%; $p=0.49$). *Proximal adjacent level stenosis* was also more common after DF compared to DA (44% vs 17%; $p<.001$). *Restenosis* at the operated level was less common after fusion (9%), than decompression alone (4% vs 14%; $p=0.04$). The slip increase after DA was found to be 1.1 mm, regardless of the presence of pre-operative DS.

Table 12. Baseline Characteristics of the Patients.

	Without spondylolisthesis		With spondylolisthesis	
	Fusion (N=44)	Decompression (N=48)	Fusion (N=59)	Decompression (N=60)
Age — years	65 ± 9	65 ± 8	67 ± 7	67 ± 7
Female sex — n (%)	26 (59)	25 (52)	44 (75)	50 (83)
Smoker — n (%)	7 (16)	8 (17)	9 (16)	8 (14)
ASA score — n (%)				
1 or 2	36 (82)	40 (87)	48 (83)	45 (76)
3	8 (18)	6 (13)	10 (17)	14 (24)
ODI	43 ± 16	40 ± 15	41 ± 13	41 ± 13
EQ-5D	0.39 ± 0.32	0.37 ± 0.31	0.37 ± 0.31	0.36 ± 0.29
VAS back pain	60 ± 25	59 ± 25	64 ± 21	64 ± 23
VAS for leg pain	65 ± 19	60 ± 24	64 ± 22	65 ± 23
Vertebral slip - mm	1.7 ± 2.3	0.6 ± 1.4	7.4 ± 2.8	7.4 ± 3.1
Levels of surgery				
1	22 (50)	27 (56)	41 (69)	39 (65)
2	22 (50)	21 (44)	18 (31)	21 (35)
Stenosis grade operated level(s)			(N=58)	
Area ≤ 75 - n (%)	40 (91)	46(96)	56 (97)	57 (95)
Schizas C-D, n (%)	38 (88) N=43	41 (85)	51 (88)	51 (85)
Mean dural sac area - mm ²	43 ± 18	41 ± 18	38 ± 15	41 ± 17
Disc degeneration adjacent level			N=58	
Type I — n (%)	0 (0)	1 (2)	0 (0)	0 (0)
Type II — n (%)	3 (7)	4 (8)	2 (3)	6 (10)
Type III — n (%)	20 (45)	18 (38)	23 (40)	24 (40)
Type IV — n (%)	19 (43)	20 (42)	29 (50)	30 (50)
Type V — n (%)	2 (5)	5 (10)	4 (7)	0 (0)
Method for surgery				
Bilateral laminotomies		10 (21)		12 (20)
Central decompression		38 (79)		48 (80)
Uninstrumented posterolateral fusion (PLF)	2 (5)		4(7)	
Instrumented PLF	41 (93)		51 (86)	
Posterior Lateral Interbody Fusion (PLIF)	1 (2)		4 (7)	
Stenosis grade adjacent level	(N=40)	(N=44)	(N=51)	(N=51)
Area ≤ 75mm ² — n (%)	3 (8)	4 (9)	2 (4)	3 (6)
Schizas C-D, n (%)	1 (3) N=39	3 (7)	0 (0)	2 (4)
Mean dural sac area-mm ²	126 ± 38	123 ± 37	130 ± 34	138 ± 46

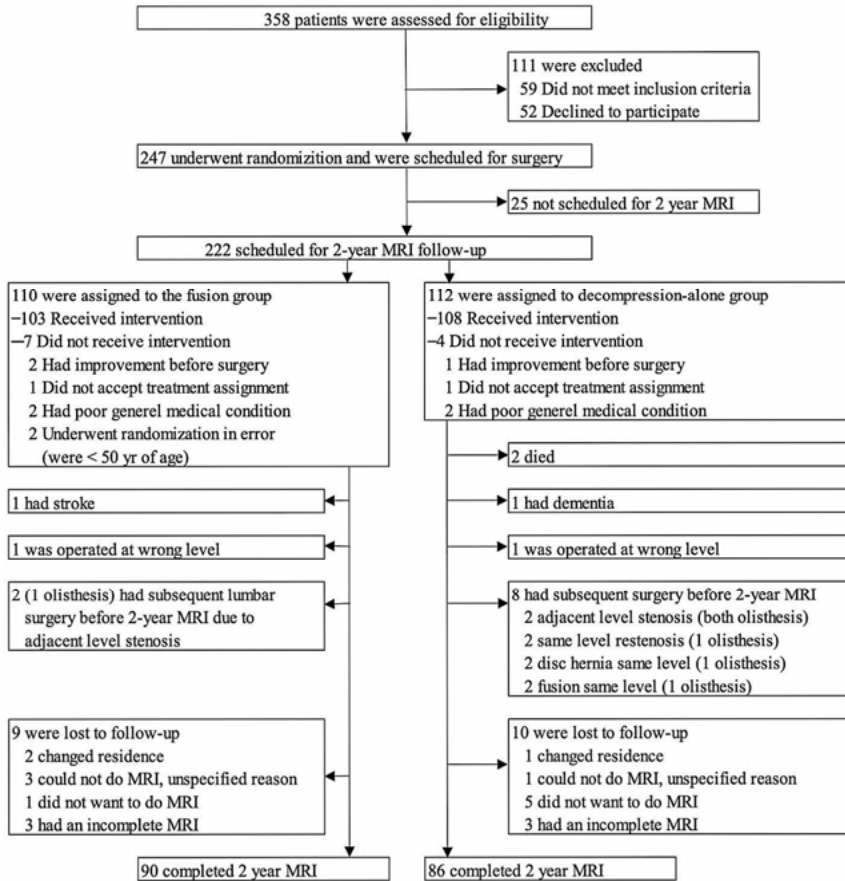


Figure 10. Enrolment, randomization, and treatment at two-year follow-up.

Table 13. Radiological outcomes at two years.

	All patients			Without spondylolisthesis			With spondylolisthesis		
	DF	D	P-Value	DF	D	P-Value	DF	D	P-Value
MRI	(N=90)	(N=86)		(N=38)	(N=40)		(N=52)	(N=46)	
Restenosis or/and adjacent level stenosis									
Dural Sac Area ≤ 75 – n (%)	42 (47)	25 (29)	0.02	17 (45)	14 (35)	0.49	25 (48)	11 (24)	0.02
Dural Sac Morphology (Schizas) C-D – n (%)	36 (40)	20 (23)	0.02	16 (42)	12 (30)	0.35	20 (38)	7 (15)	0.01
Proximal Adjacent level stenosis									
Dural Sac Area ≤ 75 – n (%)	40 (44)	16 (17)	<0.001	17 (45)	6 (15)	0.009	23 (44)	10 (22)	0.03
Dural Sac Morphology (Schizas) C-D – n (%)	36 (40)	13 (15)	<0.001	16 (42)	7 (18)	0.03	20 (38)	6 (13)	0.009
Restenosis at operated level									
Dural Sac Area ≤ 75 mm ² – n (%)	4 (4)	12 (14)	0.04	0 (0)	9 (22)	0.004	4 (8)	3 (7)	>0.99
Dural Sac Morphology (Schizas) C-D – n (%)	1 (1)	7 (8)	0.03	0 (0)	6 (15)	0.03	1 (2)	2 (4)	0.60
Mean Dural Sac Area – mm²									
Operated level	196	128	<0.001	199	121	<0.001	193	134	<0.001
Proximal adjacent level	94	123	<0.001	91	123	0.002	96	124	0.006
Operated level(s) and proximal adjacent level	92	99	0.24	90	94	0.62	94	104	0.23
Increase in adjacent level disc degeneration	0.067	-0.058	0.20	0.079	-0.15	0.01	0.058	0.022	.078
PLAIN RADIOGRAPHS	(N=98)	(N=94)		(N=41)	(N=43)		(N=57)	(N=51)	
Vertebral slip – mm	4.4 \pm 3.7	5.5 \pm 4.4	0.06	1.9 \pm 2.6	2.0 \pm 2.6	0.86	6.2 \pm 3.2	8.3 \pm 3.5	0.002

General discussion

This thesis addressed the diagnosis and treatment of lumbar spinal stenosis with or without degenerative spondylolisthesis. It is based on two randomized trials (UppSten and SSSS) and one cohort study (LSS with DS). In those, a total of 723 patients were included and studied.

Our results showed that at six months, surgery with decompression led to superior clinical outcome, compared to structured physical therapy and the improvement was not affected by delay of surgery (*Paper II*). EDX did not add predictive value in selecting the appropriate treatment (*Paper II*). Regarding the radiological outcomes, DA improved the spinal sagittal balance, regardless of preoperative DS (*Paper III*). Decompression provided good two-year clinical outcome in LSS with DS with low complication rate, and low subsequent surgery (*Paper IV*). New radiological stenosis was more common two years after DF than after DA in LSS with or without preoperative DS (*Paper V*).

The surgical treatment of LSS is reported to have up to 24% of side effects, whereas non-surgical regimes have none¹⁰. In the recent past several studies have tried to compare surgical and non-surgical treatment for LSS, without establishing consensus¹⁰. Lumbar stenosis is characterized by a great variation in treatment modalities, making nowadays the need of an agreement on stepped and stratified care more than essential³⁵. Thus, it is important to answer the question of which treatment for LSS is most effective and even more to predict which patients could benefit from surgery and who would not.

Malmivaara and Slätis concluded in their RCT that surgery leads to results favorable for surgery and that this advantage remains over time. The positive effect of decompression seemed however to diminish over time^{41,42}. In the same line, Weinstein et al, in their intention-to-treat analysis, found results favoring surgery in terms of the bodily pain component of the Short-Form General Health Survey (SF-36)⁷⁷. No difference was found in the physical function component of SF-36 and ODI. The as-treated analysis has revealed a superiority for surgery at three months in all their outcomes and this difference remained at two years. On the other hand, Delitto et al have found similar results between decompression and physical training for LSS and Rodrigues et al have found no significant pain improvement for the surgical treatment in

short and medium terms follow-up⁷⁸. Nevertheless, these studies were characterized by significant cross-over rates up to 50% and non-homogeneity of the treatments in the non-surgical group.

Cross-over

In our study there were *no* COs before six months. The 30 patients who chose to cross over from PT to surgery, performed that after six months. The analysis of the CO subgroup found that six months after the CO surgery there was an ODI improvement similar to those who were initially allocated to surgery. On the contrary, there was *no* improvement six months after physical therapy. The above findings support that when the patients present undecisive or in cases with severe comorbidity, delay in surgery would not affect the potential positive outcome of a future decompression.

The patients in the CO subgroup, had worse LL six months after CO surgery, compared to those who were randomized to DA. Moreover, there was no improvement neither in LL or SVA after CO surgery compared to the baseline data at inclusion and to their values before CO surgery. Here, one could argue that performing early surgery could be beneficial, but on the other hand, the power of the CO subgroup is too low to derive safe conclusions.

Neurophysiology

EDX before the interventions

We found no correlation between the baseline ODI and EDX. The components include activities and abilities without clear relation to the motor status. Thus, the absence of correlation may be an effect of the inclusion of other factors in the ODI that do not reflect the motor system function. Therefore, despite being a useful clinical tool, ODI does not necessarily relate to the neurogenic involvement of spinal stenosis.

The lack of correlation between initially perceived back pain and EDX parameters and the relation between worse leg pain and more favorable EMG findings indicates that the pain measured with the NRS has no relation to initial motor nerve abnormality in this patient group.

There was a significant correlation between 6MWT and EDX parameters at baseline. Shorter 6MWT was related to a greater EDX abnormality. This could be considered expected as walking directly depends on motor nerve status; spinal stenosis patients suffer from weakness and muscle fatigue⁷⁹. These findings indicate that the 6MWT could be used as an approximative measure of

the motor nerve status; however, since the parameters had great spread, the individual nerve status is better measured with EDX methods.

EDX after the interventions

On an individual level, there was no relation between the difference in ODI and EDX results after surgery. Therefore, changes in ODI after surgery cannot be related to a change in neurogenic involvement measured with the present methods. However, in the PT group, there was a relation between the difference in ODI and the difference in EMG score; worsening of ODI had a relation with the worsening of EMG and vice versa. The parameters showed great spread making it difficult to draw practical conclusions.

The perceived leg and back pain were reduced after surgery on a group level but not on the individual level as measured by EDX. In the PT group, back pain was not improved on a group level; however, there was a borderline relation of difference in back pain and EMG score after PT. Worsening back pain may relate to worsening the EMG score. This may implicate that the motor nerve involvement, which is increased due to PT, could relate to pain propagation from local structures of the back.

There were signs of discrete loss of motor neurons for both groups, whereas on an individual level, we noticed that the less initial abnormal parameters had worsened after intervention and vice versa. This finding indicates that there is no pronounced loss of motor neurons during surgery or PT. The relation of active denervation to the degree of neurogenic involvement did not change after the interventions. This could implicate that intervention does not stop the denervation/reinnervation, but the small percentage of present active denervation (9%) makes this conclusion uncertain, as a result of the low power for this analysis.

Sagittal Balance

Our radiological results in Paper III were in line with previous studies, concluding that surgery for LSS improves the spinal sagittal balance^{45,80-83}. In most LSS cases, spine extension exacerbates the symptoms whereas flexion temporarily lessens them. A typical LSS patient presents usually with severe difficulty in walking balanced and prefers to lean forward to relieve the symptoms^{84,85}. On the other hand, as cycling promotes a flexed spine position, stenosis patients can cycle, often without difficulties. Lumbar spinal stenosis is often associated with decreased lordosis, increased SVA and sagittal imbalance⁸⁶. As decompression provides the spinal roots with the required space, the patients would not need the forward flexed posture to remove the pressure from the nerves.

The spine sagittal balance and its relations are expressed through several parameters and examinations. Besides lumbar lordosis and sagittal vertebral axis, other parameters include the pelvic incidence, the pelvic tilt and the sacral slope. The measurement of the first two needs clear visualization of the femoral heads, and this can sometimes make the repeatability of the measurements difficult if the quality of the radiographies is not satisfactory. For this reason, we chose to use LL and SVA for the evaluation of the sagittal balance, as in studies of the past^{45,80-83}.

The role of degenerative spondylolisthesis

Up to some years ago, degenerative spondylolisthesis was considered as an unstable situation, and that fusion was regarded necessary when decompressing this patient group. The rationale was that decompression, especially without preservation of the midline structures, would increase instability and a fusion could prevent further slip and re-stenosis^{47,48,87}. This belief is mainly based on older studies with questionable validity^{47,48,88,89}. The above hypothesis has no scientific evidence as proper and realistic biomechanical studies are difficult to perform. The use of dynamic plain radiographies does not add evidence-based value to the assessment of instability as it is associated with a wide range of measurement errors^{51,90,91}. Several recent studies and reviews have found no clear superiority in adding fusion to decompression for standard DS cases and minimally invasive surgical techniques have shown comparable results to open decompression^{46,49,53,92-102}. A scoring system was recently published to guide decision-making when choosing decompression with fusion or minimally invasive decompression for degenerative spondylolisthesis¹⁰³. Gradually, the non-inferiority of DA compared to DF is becoming more obvious worldwide.

Our results in Paper IV showed that the presence of preoperative DS did not affect the radiological outcome, which was in favor of decompression surgery. This is in line with recent evidence that support the concept that instability in LSS with DS is often overestimated and that adding fusion to decompression for LSS does not lead to superior clinical or radiological outcome compared to DA^{46,50,53,95,98,100,104-107}. An interesting observation in our study was that in the DS subgroup, there was an increase of DS after PT. Besides the possibility of measurement error, a possible explanation could be the decrease of LL and increase of SVA in this group¹⁰⁸.

A negative consequence of fusion the acceleration of the degenerative process in the proximal segments, the so-called Adjacent Segment Disease (ASD)^{109,110}. Risk factors for ASD after fusion have been shown to be LSS as the indication for fusion and high age¹¹¹. Therefore, it is common for patients

who have previously undergone fusion for LSS with DS, to present with new degeneration and stenosis of the proximal adjacent level¹¹²⁻¹¹⁵.



Figure 11. Degeneration of L2-L3 (proximal adjacent segment) two years after decompression and fusion of L3-L5.

In Paper V, we showed that fusion increases the risk of a new stenosis at the adjacent level more than it prevents restenosis and increased slippage at the operated level and that preoperative DS is not a predictor of need for fusion. Thus, even older patients with comorbidity could benefit from a simple decompression instead of getting a fusion or being denied surgery due to high risk for complications. Other disadvantages of adding fusion include longer operating times, increased perioperative bleeding, extended hospitalization, higher risk for severe complications and elevated costs^{14,46,94,97,116,117}.

Nevertheless, even if DA provides similar clinical outcome to DF, there are LSS cases where fusion is both appropriate and desirable. In cases of stenosis with involvement of the neuroforamen where the patient has an associated rhizopathy pain from the affected nerve root, a facetectomy needs to be performed to achieve a proper decompression. Biomechanical studies have showed that the facet joints complex accounts for 40% of the segment stability¹¹⁸. Obviously, its removal would lead to instability and thus a fusion is necessary⁹⁶. Another indication for stabilization when decompressing LSS is the presence of severe deformity such as coronal imbalance or isthmic spondylolisthesis. In such cases adding a fusion could prevent the progress of the deformity^{119,120}.

In summary, our results support that the value of DS has been overestimated in the last decades. The finding of degenerative spondylolisthesis itself should probably not affect the choice of treatment method. Hence, standard cases of stenosis with DS could be treated like all other LSS.

Conclusions

The major findings of the thesis are:

1. Surgery with decompression leads to superior clinical outcome compared to structured physical therapy, at six months follow-up. Delay in surgery (cross-over) did not affect this improvement.
2. Electrodiagnosis does not add predictive value in patient selection in LSS.
3. Decompression improves the spinal sagittal balance in LSS, regardless of the presence of preoperative DS.
4. Decompression provides good two-year clinical outcome in LSS with DS. The rate of intra- and postoperative complications, and subsequent surgery is low.
5. New stenosis on two-year MRI is less common after decompression alone than after decompression with fusion in LSS with or without preoperative degenerative spondylolisthesis.

Limitations & Strengths

This thesis is based on two randomized trials (UppSten and SSSS) and one cohort study (LSS with DS). In those, a total of 723 patients were included and studied. Another major strength is the use of a national quality registry (Swespine) which provided meticulous follow-up and well-validated PROMs. The randomization process was efficient, producing groups similar at their baseline. As for all clinical studies, loss to follow-up is always an inevitable issue. Moreover, the study populations were selected by strict inclusion and exclusion criteria, and this may limited the external validity. However, in our trials, the criteria were chosen to represent the most typical LSS patient who is eligible for surgery.

The Uppsala Spinal Stenosis Trial

The trial was partially conducted during the covid-19 pandemic¹²¹. This fact caused some unavoidable increase in the waiting times, both for surgery and follow-ups. The latter may have affected, in some degree, the outcome evaluation. Another possible limitation is the short FU period that is included in the current work (Paper II, III). Nevertheless, at six months, there were no cross-overs which adds an important strength to the study. The large proportion of CO has been a methodological issue in previous spinal stenosis trials, thus making analysis and conclusions difficult^{35,39}. UppSten is, to the best of our knowledge, the first RCT comparing surgical and non-surgical treatment for LSS with evaluation of different dimensions based on clinical, radiological, neurophysiological and laboratory outcome. The large number of the included patients add another strength to this trial. Moreover, the treatment in the PT group was homogenous and all patients received the same structured treatment regime. The option to cross-over allowed us to study the CO subgroup further. Finally, the evaluation of the DS was made on standing lateral whole spine plain radiographs and not on supine MRI.

Cohort Study

The observational character of the study could lead to limitations such as missing outcome measures at follow-up and heterogeneity in surgical techniques and postoperative strategies. However, previous research has found no correlation between non-responders and worse outcome¹²². On the other hand, the study included a large number of patients with a good follow-up rate.

The Swedish Spinal Stenosis Study

A potential weakness is that dynamic radiographs were not used, which means that we may have underestimated the spondylolisthesis and included patients with so called intervertebral instability who would have been excluded from other studies^{35,48,92}. Nevertheless, the concept of degenerative spinal instability has been difficult to define, and the usefulness of dynamic radiographs has been questioned, as the relationship between instability and symptoms is far from clear-cut¹²³. Another possible limitation is that the cut-offs for radiological stenosis, dural sac area ≤ 75 mm², and dural sac morphology Schizas grades C-D are validated for preoperative MRI but not for two-year MRI. Index level restenosis may in some cases has been caused by inadequate primary decompression rather than actual recurrent stenosis. If this is the case, we have no reason to believe this to be more common in the decompression with fusion group, therefore it should not have affected our results and conclusions. Besides DS, there are other factors which could indicate need for fusion and that have not been analyzed. This may lead to the identification of subgroups that could benefit from fusion, such as developmental stenosis which is caused by pre-existing short pedicles and a narrow bony spinal canal and that was not assessed on MRI^{124,125}. Nevertheless, the study included a large number of patients with a high follow-up rate. To our knowledge, there are no other trials with two-year MRI follow-up after LSS surgery.

Clinical implications and future studies

Until recently there has been an absence of consensus regarding the treatment of LSS¹⁰. By showing a clear advantage in favor of surgery, this thesis added useful knowledge to the therapy arsenal of spinal stenosis.

The aging of the global population, and the need for guidelines in LSS treatment, add more value to the current study. Moreover, as surgery with decompression alone leads to similar clinical and superior radiological outcome, long and high-risk fusions could be avoided.

Previous trials on connective tissue and blood samples have shown that specific molecules are upregulated in inflammatory conditions¹²⁶⁻¹²⁸. Changes in the connective tissue that cause LSS are mainly inflammatory¹²⁹. The Uppsala Spinal Stenosis Trial includes a laboratory outcome, where blood samples and the flavum ligament will be examined. This could lead to a more unifying picture of the LSS pathomechanism and to the development of new treatments to be used instead of or in combination with surgery. The laboratory outcome will be presented in the near future and is not included in this thesis.

Sammanfattning på svenska (summary in Swedish)

Introduktion

Lumbal spinal stenosis (LSS), trängsel i ländryggradskanalen, karakteriseras av smärta i rygg och ben, gångsvårigheter och ofta domningar i ben och fötter samt ostadighet i kombination med försämrad balans. Tillståndet orsakas av åldersförändringar i ländryggen i form av buktande diskar, pålagringar kring lederna och förtjockade ledband. Allt detta tillsammans ger trängsel i nervkanalen med påverkan på nerverna. LSS drabbar äldre och är ovanligt hos personer som är yngre än 50 år. Diagnosen får alltmer intresse med en åldrande befolkning och högre krav på fortsatt aktivitet. LSS är den vanligaste indikationen för ryggkirurgi. Den kirurgiska behandlingen innebär avlastning av nervstrukturerna i det trånga området. Operationen sker i narkos genom ett litet snitt på baksidan av ländryggen. Därefter avlägsnas förtjockade ledband och delar av leder, pålagringar och kotbågar, så kallad dekompression. Tidigare studier har visat att kirurgi ger ett bättre resultat än icke-kirurgisk behandling. Metodologiska problem gör dock att det fortfarande finns oklarheter i om kirurgi generellt sett är att föredra.

Efter kirurgi 60–70% av patienterna rapporterar sig vara nöjda med resultatet och en mindre andel upplever ingen förbättring av kirurgen. Icke-kirurgisk behandling har, i vissa studier, visat på ett gott resultat medan andra studier har visat på att fördelen med kirurgisk behandling avtar med tiden. Fysisk aktivitet på motionscykel kan minska behovet av kirurgi. Dessutom har kirurgi i sig en positiv placeboeffekt som kan förbättra symptom i vissa sjukdomar.

Det har spekulerats i om trängseln för nerverna hos vissa patienter ger en permanent nervskada. Resultat från nervundersökningar har visat sig ha ett möjligt prediktivt värde för naturalförloppet vid LSS.

Det debatteras bland ryggkirurger kring behovet av att som tillägg till dekompressionen göra omfattande korrektion och steloperation för att återskapa den balansen som succesivt försämras på grund av åldersrelaterade förändringar i

ländryggen. Dessutom, vid LSS med kotglidning (spondylolistes), att komplettera dekompressionen med steloperation har inte visat sig ge ett bättre resultat än enbart dekompression.

Denna avhandling inkluderar analys av totalt 723 patienter. Syftet var först och främst att utvärdera om kirurgi med dekompression ger ett bättre resultat än icke kirurgisk behandling med strukturerad träning. Den viktigaste sekundära frågeställningen var att undersöka om graden av påverkan på nervstrukturerna mätt med nervundersökningar påverkar resultatet av kirurgi. Skulle man med nervundersökningar kunna förutsäga vilka patienter som har förutsättningar att gagnas av kirurgi skulle många patienter kunna avrådas från operation och de risker ett ingrepp innebär. Avhandlingen undersökte om dekompression ger bättre balans i ryggen. Till slut, målet vara att kartlägga frekvensen av komplikationer samt behov av ytterligare kirurgi vid LSS med kotglidning och att utvärdera hur vanligt det är med ny stenosis efter kirurgi.

Avhandlingen baseras på två stora randomiserade studier – Uppsala Spinal Stenosis Studie och Svenska Spinal Stenosis Studie, samt på Kohortstudien om spinal stenosis med degenerativ glidning.

Studie I

Detta delarbete beskriver UppStens protokoll, uppläggning samt planerade analyser. UppSten är en klinisk randomiserad studie med initialt planerade 150 patienter. Deltagare skulle lottas till två behandlingsarmar. I den första, opereras patienterna med dekompression (grupp A) och i andra armen är behandlingen strukturerad träning på motionscykel enligt ”Östersundsmodellen” (grupp B). Uppföljning görs efter sex månader, ett år, två år och fem år. De patienter från grupp B som inte var nöjda med resultatet kunde flytta till grupp A och bli opererade (s.k. cross-over, CO).

Studie II

I detta delarbete, analyseras och presenteras de sex-månaders kliniska och neurofysiologiska resultat av studien UppSten. Studien inkluderade patienter mellan 2018–2021. För att kompensera oundvikligt bortfall, randomiserades totalt 155 patienter, 79 till kirurgi och 76 till fysioterapi gruppen. Vid sex månader, visades det att kirurgi jämfört med fysioterapi ledde till bättre resultat i alla kliniska mått förutom ångestskalan. Patienter i CO-subgruppen förbättrades också efter CO-operation i samma utsträckning som för de patienter som lottades till operation från början. Den neurofysiologiska analysen kunde inte

stödja att sådana undersökningar skulle kunna användas som urvalsverktyg för vilka patienter skulle ha nytta av kirurgi vid spinal stenos i ländryggen.

Studie III

Patienter med lumbal spinal stenos har en tendens att gå framåt lutade. Detta görs för att vidga den redan trånga spinalkanalen och avlasta under en kort stund deras besvär. Den här positionen orsakar dock en påverkan på ryggens balans. Det tredje delarbetet, som analyserar patienter från studien UppSten, undersöker om kirurgi är effektivare än fysioterapi gällande balansen. Sex månader efter behandlingarna visade resultaten att operation med dekompression gav en förbättrad spinal balans vilket inte var fallet efter strukturerad fysioterapi. Resultaten påverkades inte av eventuell glidning innan kirurgin.

Studie IV

Projektet avser en observationsstudie med 346 patienter med spinal stenos och degenerativ glidning som opererades med dekompression utan steloperation. Samtliga patienter opererades mellan 2012–2017 på Capio Spine Center Stockholm, en stor ryggkirurgisk enhet med högt patientflöde. Resultatet visade att kirurgi med dekompression ger en signifikant klinisk förbättring efter två år samt att komplikationsfrekvens och frekvensen av ytterligare kirurgi är låg. Studiens konklusion är att dekompression är effektiv och säker för spinal stenos med glidning.

Studie V

Det sista delarbetet presenterar de radiologiska två-årsresultat av den Svenska Spinal Stenos Studien. Studien var en randomiserad klinisk studie som inkluderade 222 patienter med spinal stenos med eller utan glidning. Patienterna lottades mellan kirurgi med dekompression eller kirurgi med dekompression och fusion (steloperation). Studien var aktiv mellan 2012–2016 och ägde rum på fyra offentliga och två privata sjukhus i Sverige. Resultatet visade att fusionen ökar risken för en ny spinal stenos på magnetkameraundersökning två år efter kirurgi. Detta stödjer evidensen att vid spinal stenos, med eller utan glidning, är kirurgi med dekompression att föredra.

Slutsatser

1. Kirurgi med dekompression ger vid sex månader, ett bättre kliniskt resultat jämfört med strukturerad fysioterapi. Fördröjning av operation (cross-over) påverkade inte denna förbättring.
2. Det finns inte tillräckligt med stöd att neurofysiologi kan användas vid urvalet av patienter till kirurgi.
3. Dekompression leder till en bättre hållning så att stenoserade patienter kan gå rakare efter operation utan att behöva böja sig fram.
4. Vid spinal stenos med kotglidning, ger dekompression bra kliniska resultat med låg komplikationsfrekvens och låg frekvens av ytterligare kirurgi.
5. Dekompression med samtidigt fusion ökar risken för en ny radiologisk stenos två år efter operation.

Περίληψη στα Ελληνικά (summary in Greek)

Εισαγωγή

Η στένωση της οσφυϊκής μοίρας της σπονδυλικής στήλης (ΟΣΣ) χαρακτηρίζεται από πόνο στη ράχη και κυρίως νευρογενή διαλείπουσα χωλότητα με πόνο, κράμπες και μουδιάσματα στα κάτω άκρα, δυσκολία στο βάδισμα και συχνά διαταραχές της ισορροπίας και αστάθεια. Η πάθηση προκαλείται από εκφυλιστικές αλλοιώσεις στην οσφυϊκή μοίρα με τη μορφή διογκωμένων μεσοσπονδύλιων δίσκων, οστεοφύτων γύρω από τις αρθρώσεις και υπερπλασία των συνδέσμων. Ο συνδυασμός αυτός προκαλεί σταδιακά στένωση στο σπονδυλικό σωλήνα με προοδευτική πίεση στα νεύρα. Η ΟΣΣ παρουσιάζεται συνήθως σε ασθενείς μεγαλύτερης ηλικίας και σπανίζει σε άτομα κάτω των 50 ετών. Καθώς ο πληθυσμός γηράσκει και ταυτόχρονα αποκτά όλο και υψηλότερες απαιτήσεις για έναν πιο δραστήριο τρόπο ζωής, η σπονδυλική στένωση κερδίζει ολοένα το ενδιαφέρον της παγκόσμιας ιατρικής κοινότητας.

Η ΟΣΣ αποτελεί τη συνηθέστερη χειρουργική ένδειξη στη σπονδυλική στήλη. Η επέμβαση γίνεται ανοιχτά, ελάχιστα επεμβατικά ή και ενδοσκοπικά. Σκοπός είναι η αφαίρεση των δομών που ασκούν πίεση στις νευρικές ρίζες (αποσυμπίεση). Προηγούμενες μελέτες έχουν δείξει ότι η χειρουργική αντιμετώπιση της στένωσης πλεονεκτεί έναντι της μη χειρουργικής θεραπείας. Παρόλα αυτά λόγω μεθοδολογικών προβλημάτων και δυσκολιών, τα αποτελέσματα ήταν αμφίβολα.

Μετά την επέμβαση, το 70% των ασθενών αναφέρει ότι είναι ικανοποιημένο με τα αποτελέσματα ενώ ένα μικρότερο ποσοστό δε παρουσιάζει βελτίωση. Η μη χειρουργική θεραπεία σε ορισμένες μελέτες έχει παρουσιάσει θετικά αποτελέσματα ενώ άλλες έρευνες έχουν δείξει ότι το όφελος της επέμβασης μειώνεται με την πάροδο του χρόνου. Η σωματική δραστηριότητα σε στατικό ποδήλατο γυμναστικής μπορεί σε κάποιες περιπτώσεις να μειώσει την ανάγκη για χειρουργική αντιμετώπιση. Επιπλέον, η ίδια η επέμβαση έχει θετική επίδραση εικονικού φαρμάκου (placebo) που μπορεί να βελτιώσει τα συμπτώματα σε ορισμένες ασθένειες.

Η συμπίεση νEURΩΝ σε ορισμένους ασθενείς θεωρείται ότι προκαλεί μόνιμη βλάβη. Αποτελέσματα από νευροφυσιολογικές (ΝΦ) μελέτες έχουν δείξει σημαντικό ρόλο της νευροφυσιολογίας στην πρόγνωση της σπονδυλικής στένωσης.

Προηγούμενες κλινικές μελέτες έχουν συμπεράνει ότι μετά από επέμβαση αποσυμπίεσης, συχνά βελτιώνεται και ο πόνος στη μέση (οσφυαλγία). Πολλοί ασθενείς αναφέρουν επιπλέον βελτιωμένη στάση σώματος (οβελιαία ισορροπία) μετά από αποσυμπίεση. Η προσθήκη σταθεροποίησης (σπονδυλοδεσία) στη χειρουργική αποσυμπίεση έχει συζητηθεί και μελετηθεί πολύ στο παρελθόν. Πρόσφατες έρευνες έχουν δείξει ότι σε τυπικές περιπτώσεις στένωσης, η αποσυμπίεση και μόνο αρκεί, ακόμα και εάν υπάρχει ταυτόχρονη εκφυλιστική σπονδυλολίσηση.

Η παρούσα διατριβή εξέτασε και ανέλυσε συνολικά 723 ασθενείς. Σκοπός ήταν πρώτα και κύρια να αξιολογήσει εάν η χειρουργική επέμβαση με αποσυμπίεση δίνει καλύτερα αποτελέσματα από τη μη χειρουργική θεραπεία, με φυσιοθεραπεία στο στατικό ποδήλατο. Επιπλέον, να διερευνήσει εάν ο βαθμός επίδρασης της στένωσης στις νευρικές δομές, όπως υπολογίζεται με ΝΦ μεθόδους, επηρεάζει το αποτέλεσμα της χειρουργικής επέμβασης. Εάν η ΝΦ εξέταση μπορούσε να χρησιμοποιηθεί ώστε να προβλέψει ποιοί από τους ασθενείς έχουν τις προϋποθέσεις να επωφεληθούν από τη χειρουργική επέμβαση, πολλοί ασθενείς θα μπορούσαν αποφύγουν το χειρουργείο και τους κινδύνους που αυτό συνεπάγεται.

Η διατριβή αυτή βασίζεται σε δύο μεγάλες τυχαιοποιημένες μελέτες (randomized controlled trials– RCTs) και μία μελέτη σειράς (cohort): τη Μελέτη Σπονδυλικής Στένωσης της Ουψάλας (Uppsala Spinal Stenosis Trial – UppSten), τη Σουηδική Μελέτη Σπονδυλικής Στένωσης (Swedish Spinal Stenosis Study – SSSS), και τη Μελέτη Σπονδυλικής Στένωσης με Εκφυλιστική Σπονδυλολίσηση.

Μελέτη I

Περιγράφει το πρωτόκολλο, τη διάταξη και τις προγραμματισμένες αναλύσεις της UppSten. Η UppSten είναι μια κλινική τυχαιοποιημένη μελέτη με αρχικά 150 ασθενείς. Οι συμμετέχοντες κατανέμονται τυχαία σε δύο ομάδες θεραπείας. Στη πρώτη οι ασθενείς χειρουργούνται με αποσυμπίεση (ομάδα Α), και στη δεύτερη η θεραπεία περιλαμβάνει δομημένη φυσιοθεραπεία σε ποδήλατο άσκησης σύμφωνα με το "μοντέλο Östersund" (ομάδα Β). Η παρακολούθηση γίνεται μετά από έξι μήνες, ένα, δύο και πέντε έτη. Όσοι ασθενείς από την ομάδα Β δεν είναι ικανοποιημένοι με το αποτέλεσμα, μπορούν να μεταπηδήσουν στην ομάδα Α και να υποβληθούν σε χειρουργική επέμβαση (cross-over, CO).

Μελέτη II

Σε δημοσίευση αυτή, αναλύονται και παρουσιάζονται τα κλινικά και νευροφυσιολογικά αποτελέσματα της UppSten, στους έξι μήνες. Η μελέτη περιλάμβανε ασθενείς μεταξύ 2018-2021. Για να αντισταθμιστεί αναπόφευκτη απώλεια, συμπεριλήφθηκαν συνολικά 155 ασθενείς, 79 κατανεμήθηκαν τυχαία στη χειρουργική ομάδα, και 76 στην ομάδα φυσιοθεραπείας. Στους έξι μήνες, αποδείχθηκε ότι η χειρουργική επέμβαση σε σύγκριση με τη φυσικοθεραπεία, οδήγησε σε σαφώς καλύτερα αποτελέσματα σε όλες τις κλινικές μετρήσεις εκτός από την κλίμακα άγχους. Οι ασθενείς που επέλεξαν cross-over βελτιώθηκαν επίσης μετά από την επέμβαση CO στον ίδιο βαθμό όπως και οι ασθενείς που κατανεμήθηκαν από την αρχή στην χειρουργική ομάδα. Τα αποτελέσματα της ΝΦ ανάλυσης κατέληξαν ότι δεν υπάρχουν αρκετές ενδείξεις ώστε η ΝΦ εξέταση να μπορούσε να χρησιμοποιηθεί ως εργαλείο επιλογής για το ποιοι οι ασθενείς θα επωφεληθούν από τη χειρουργική επέμβαση για ΟΣΣ.

Μελέτη III

Οι ασθενείς με σπονδυλική στένωση τείνουν να βαδίζουν με πρόσθια κάμψη του σώματος. Έτσι, διεγύρεται προσωρινά ο στενωτικός σπονδυλικός σωλήνας το οποίο οδηγεί σε προσωρινή ανακούφιση των συμπτωμάτων. Ωστόσο, αυτή η θέση έχει αρνητικό αντίκτυπο στην ισορροπία της σπονδυλικής στήλης και του σώματος.

Η τρίτη μελέτη αναλύει ασθενείς από την UppSten και εξετάζει εάν η χειρουργική επέμβαση είναι πιο αποτελεσματική από τη φυσιοθεραπεία στη βελτίωση της οβελιαίας ισορροπίας. Έξι μήνες μετά τις θεραπείες, η αποσυμπίεση βελτίωσε με σημαντική διαφορά την ισορροπία της σπονδυλικής στήλης σε σύγκριση με τη φυσικοθεραπεία. Τα αποτελέσματα δεν επηρεάστηκαν από ενδεχόμενη προεγχειρητική σπονδυλολίσηση.

Μελέτη IV

Η δημοσίευση αφορά σε μελέτη παρατήρησης με 346 ασθενείς με σπονδυλική στένωση και ταυτόχρονη εκφυλιστική σπονδυλολίσηση που αντιμετωπίστηκαν με αποσυμπίεση χωρίς σπονδυλοδεσία. Όλοι οι ασθενείς χειρουργήθηκαν μεταξύ 2012-2017 στο Carpio Spine Center Stockholm, μια μεγάλη κλινική σπονδυλικής στήλης με υψηλή ροή ασθενών. Τα διετή αποτελέσματα έδειξαν ότι η αποσυμπίεση οδηγεί σε μεγάλη κλινική βελτίωση και ότι το ποσοστό επιπλοκών και η συχνότητα περαιτέρω χειρουργικών επεμβάσεων είναι χαμηλά. Το συμπέρασμα της μελέτης είναι ότι η αποσυμπίεση είναι αποτελεσματική και ασφαλής μέθοδος για τη σπονδυλική στένωση με ολίσηση.

Μελέτη V

Εδώ παρουσιάζονται τα ακτινολογικά διετή αποτελέσματα της Σουηδικής Μελέτης Σπονδυλικής Στένωσης. Η μελέτη ήταν μια τυχαιοποιημένη κλινική έρευνα που περιέλαβε 222 ασθενείς με σπονδυλική στένωση με ή χωρίς ολίσθηση. Ήταν ενεργή μεταξύ 2006-2012 και διεξήχθη σε τέσσερα δημόσια και δύο ιδιωτικά νοσοκομεία στη Σουηδία. Οι ασθενείς τυχαιοποιήθηκαν μεταξύ αποσυμπίεσης και αποσυμπίεσης με σπονδυλοδεσία. Τα αποτελέσματα έδειξαν ότι η σπονδυλοδεσία αυξάνει τον κίνδυνο μιας νέας στένωσης δύο χρόνια μετά την επέμβαση.

Συμπεράσματα

1. Η χειρουργική επέμβαση με αποσυμπίεση οδηγεί σε καλύτερα κλινικά αποτελέσματα σε σύγκριση με τη δομημένη φυσιοθεραπεία. Η βελτίωση δεν επηρεάστηκε από ενδεχόμενη καθυστέρηση (cross-over).
2. Δεν υπάρχουν επαρκείς ενδείξεις ότι η νευροφυσιολογική εξέταση μπορεί να χρησιμοποιηθεί για την επιλογή ασθενών για χειρουργική επέμβαση.
3. Η αποσυμπίεση οδηγεί σε καλύτερη στάση του σώματος και ασθενείς μπορούν να βαδίζουν χωρίς να χρειάζεται να σκύβουν προς τα εμπρός.
4. Στη σπονδυλική στένωση με ολίσθηση, η αποσυμπίεση δίνει καλά κλινικά αποτελέσματα με χαμηλό ποσοστό επιπλοκών και μικρή συχνότητα πρόσθετων χειρουργικών επεμβάσεων.
5. Η αποσυμπίεση με ταυτόχρονη σπονδυλοδεσία αυξάνει τον κίνδυνο μιας νέας ακτινολογικής στένωσης δύο χρόνια μετά την επέμβαση.

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