# PhD thesis

Christian C. Støttrup

Christian.Stottrup@rsyd.dk

Spine Center of Southern Denmark

Lillebaelt Hospital

Østre Hougvej 55

DK-5500 Middelfart

Department of Regional Health Research

Faculty of Health Sciences

University of Southern Denmark

Winsløwparken 19, 3.

DK-5000 Odense C

# Quantitative Sensory Testing and PET/CT Scanning in Assessment of Surgical Outcome for Lumbar Disc Herniation

PhD thesis by Christian C. Støttrup

*Spine Center of Southern Denmark – part of Lillebaelt Hospital*

*Department of Regional Health Research – University of Southern Denmark*

*Middelfart, February 2020*

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# Preface

Three years of cumbersome academic work including teaching of undergraduate students, multiple courses in different fields and not least, the joy of funding your own research through research grant proposals. Those are the delights that are part of the path to a PhD candidacy.

**So why would anyone do a PhD study?**

Inspired by Albert Einstein, philanthropist Armand Hammer once said:

*"It is the responsibility of every human being to aspire to do something worthwhile, to make this world a better place than the one he found." – Armand Hammer*

I guess everyone who has achieved this academic degree has their own story and answer to why and how they came to the decision to enroll themselves as a PhD student.

This thesis is the result of a brief meeting over a cup of coffee in-between surgeries where I met Associate Professor Mikkel Ø. Andersen. Through a number of subsequent meetings, a PhD application came into form and despite some collaborators finding elements of it to be "mental masturbation" it ended up being accepted for enrollment.

Following the enrollment, I've faced many challenges, each of which has contributed to my experience and knowledge, which together with courses and hard work should now officially constitute me as "a researcher".

To recapitulate; "Do I regret my choice of becoming a PhD student?" – No. The knowledge, experiences and collaborations I've gained during my years as an academic student are invaluable and will most certainly be significant throughout the rest of both my professional and personal life.

# Acknowledgements

I would like to express my profound gratitude to all who have contributed to make this PhD candidacy possible. Great thanks should be given to colleagues and friends at the Spine Center of Southern Denmark, without your invaluable work, this thesis would never have been possible. Acknowledgement should also be given to anyone who contributed to the DaneSpine database and not least the people responsible for the existence of the database itself.

*"The only people with whom you should try to get even are those who have helped you." – John E. Southard*

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Lastly, but not least, great recognition should be given to my family, and particularly my wife, who, especially through the final months before deadline, have demonstrated extensive understanding and tolerance.

*"I can no other answer make but thanks, and thanks, and ever thanks." – William Shakespeare*

Christian C. Støttrup, February 2020

# Table of Content

# Preliminaries

## Supervisors

**Mikkel Ø. Andersen**, MD, Associate Clinical Professor (Main supervisor)

*Spine Center of Southern Denmark – part of Lillebaelt Hospital*

*Department of Regional Health Research – University of Southern Denmark*

**Søren F. O'Neill**, Chiropractor, M.Rehab., PhD, Associate Clinical Professor

*Spine Center of Southern Denmark – part of Lillebaelt Hospital*

*Department of Regional Health Research – University of Southern Denmark*

**Rikke Rousing**, MD, PhD

*Spine Center of Southern Denmark – part of Lillebaelt Hospital*

**Poul Flemming Høilund-Carlsen**, MD, DMSc, Professor

*Department of Nuclear Medicine – Odense University Hospital*

*Department of Clinical Research – University of Southern Denmark*

## Disclosures

The primary investigator, Christian C. Støttrup, has received the grants mentioned under Funding (page III). No other disclosures related to this thesis or its related publications.

The main supervisor, Mikkel Ø. Andersen, has no disclosures related to this thesis or its related publications.

Co-supervisor Søren F. O'Neill has no disclosures related to this thesis or its related publications.

Co-supervisor Rikke Rousing has no disclosures related to this thesis or its related publications.

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## Publications related to this thesis

1. Støttrup CC, Andresen AK, Carreon L, Andersen MØ **Increasing reoperation rates and inferior outcome with prolonged symptom duration in lumbar disc herniation surgery – a prospective cohort study.** *(Appendix 1)*

   The Spine Journal. September 2019. Volume 19, Issue 9, 1463 – 1469.

2. Støttrup CC, Andersen MØ, Carreon L, O'Neill SF **Utility of Preoperative Quantitative Sensory Testing in patients with Lumbar Disc Herniation.** *(Appendix 2)*

   Ready for submission. European Spine Journal.

3. Støttrup CC, Constantinescu C, Piri R, Khosravi M, Andersen MØ, Alavi A, Høilund-Carlsen PF "**Visualization" of pain using 18-FDG PET/CT of the brain.** *(Appendix 3)*

   In review by co-authors.

# Summary


## English summary

This PhD thesis examines the consequences of prolonged duration of preoperative pain, both in regards of clinical outcome of surgery and whether hypersensitization of pain perception occurs. A large retrospective cohort study including more than 2,000 patients found inferior clinical outcomes of surgical treatment in patients with delayed surgical intervention. Hypersensitivity to pain and experimental stimuli may occur in patients with lumbar disc herniation, however, no clinical importance or usefulness of such tests were detected. Unilateral pain in patients with LDH was found to be associated with increased glucose metabolism in the contralateral thalamus, suggesting a central role of thalamus in chronic pain perception.

## Danish summary

Denne ph.d.-afhandling undersøger konsekvenserne af forlænget varighed af præoperative smerter, både hvad angår det kliniske resultat af kirurgi og hvorvidt der forekommer sensibilisering af smerteopfattelsen. Et stort kohortestudie med over 2.000 patienter påviste dårligere klinisk effekt af kirurgi ved udsættelse af den kirurgiske behandling hos patienter med lumbal diskusprolaps. Hos patienter med lumbal diskusprolaps kan det ikke udelukkes at der forekommer kroniske tilstande med deraf følgende smertesensibilisering, men en klinisk konsekvens eller anvendelighed af smertetest kunne ikke påvises. Resultaterne viste en sammenhæng mellem de ensidige bensmerter som forekommer hos prolapspatienter og målinger af stofskiftet i basalganglierne (thalamus) i den modsidige hjernehalvdel. Dette kunne tyde på at basalganglierne (thalamus) spiller en vigtig rolle i bearbejdningen og opfattelsen af smerter.

## List of tables



## List of figures

## List of abbreviations

| | |
|---|---|
| BMI | Body Mass Index |
| CI | Confidence Interval |
| DaneSpine | Danish national surgical spine database |
| EQ-5D | European Quality of Life Index 5 dimensions 3 levels |
| FDG | 2-[$^{18}$F] fluoro-2-deoxy-D-glucose |
| LBP | Low Back Pain |
| LDH | Lumbar Disc Herniation |
| mSv | millisievert |
| MTGr | Mean Thalamic Glucose metabolism ratio |
| ODI | Oswestry Disability Index |
| PET/CT | Positron Emission Tomography / Computed Tomography |
| PROMs | Patient Reported Outcome measures |
| PROs | Patient Reported Outcomes |
| PVC | Partial Volume Corrected |
| QST | Quantitative Sensory Testing |
| RCT | Randomized Controlled Trial |
| ROI | Region of Interest |
| SD | Standard Deviation |
| STROBE | Strengthening the Reporting of Observational studies in Epidemiology guidelines |
| SUV | Standard Uptake Value |
| THGr | Total Hemispheric Glucose metabolism ratio |
| VAS | Visual Analogue Scale |

# Introduction

## Lumbar Disc Herniation

The human spine consists of 24 vertebrae which interconnect via the facet joints and the intervertebral discs. The primary function of this bony structure is weight-distribution and protection of the extra-cranial central nervous system. The lower portion of the spine, the lumbar region, consists of five lumbar vertebrae which, separated by intervertebral discs, bear most of the weight of the body (Figure 1). The intervertebral discs act as shock absorbers during every-day activities and consists of a though, flexible outer ring called the annulus fibrosus, and a soft, jelly-like center called the nucleus pulposus (Figure 2). With each set of vertebrae and intervertebral disc, a set of spinal nerve-roots exits the spinal canal and becomes peripheral nerves (Figure 1).

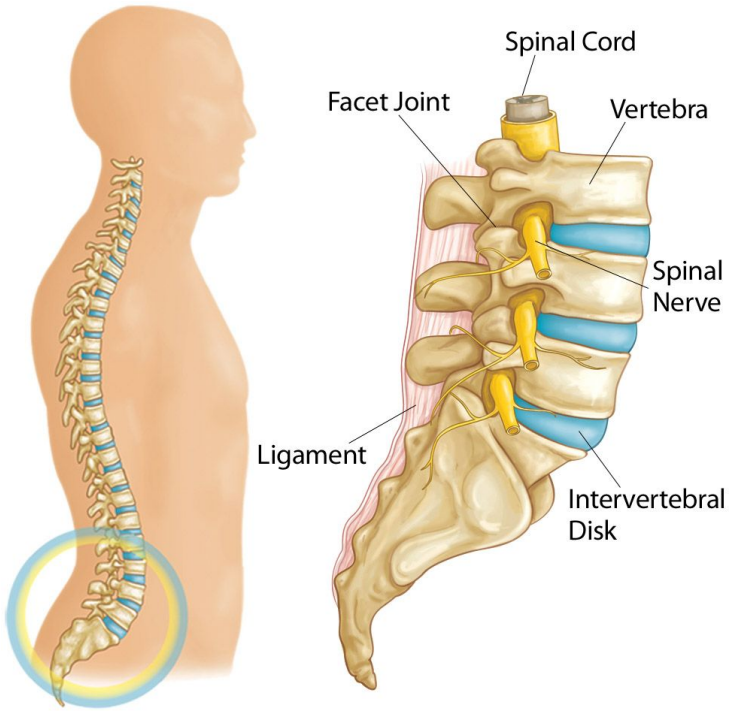


*Figure 1 – The lumbar spine with nerve-roots*
*Reproduced with permission from OrthoInfo © American Academy of Orthopaedic Surgeons. http://orthoinfo.aaos.org.*

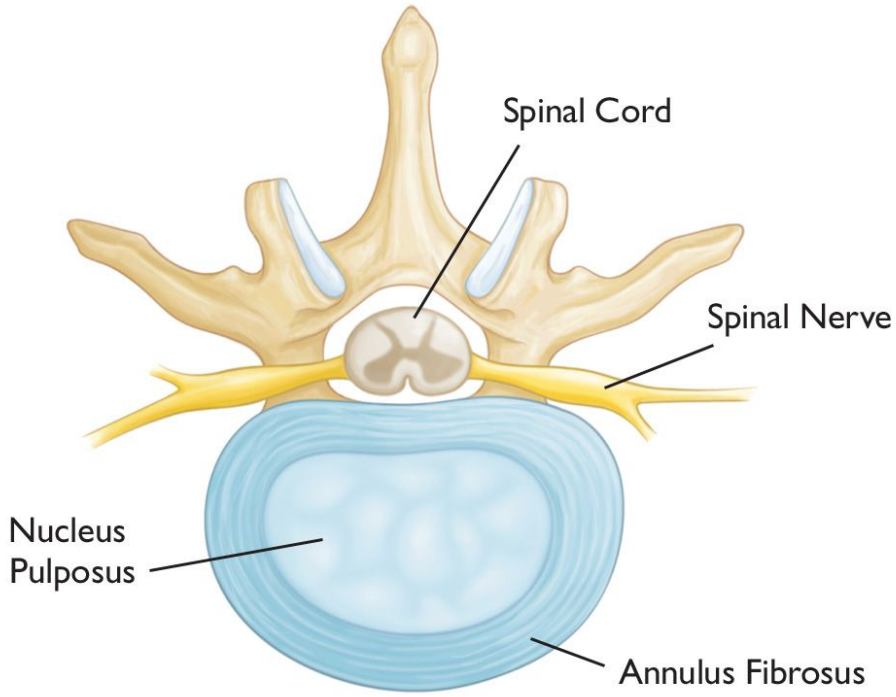


*Figure 2 – Illustration of a healthy disc with adjacent nerve-roots*
*Reproduced with permission from OrthoInfo © American Academy of Orthopaedic Surgeons. http://orthoinfo.aaos.org.*

As a result of natural, age-related wear and tear the nucleus pulposus may rupture through the annulus fibrosus, a disc herniation, and consequently exert pressure and subsequent irritation on the adjacent nerve-root (Figure 3). This may cause a combination of nerve root ischemia and inflammation, leading to neoinnervation and neovascularization, which in turn leads to both local and radicular pain (1-3). Patients with lumbar disc herniation (LDH) often experience primarily unilateral pain radiating from the lumbar region to the related dermatomal area of their leg.

LDH often occurs in otherwise healthy, self-supporting middle-aged individuals, and as a result, is associated with great morbidity and significant socioeconomic consequence for both the individual and society. The prevalence and incidence of LDH is hard to estimate as many of these cases go untreated or are treated in primary care without hospitalization. Studies by the Danish National Health Authority indicate an incidence of radicular pain due to LDH of 1-3% (4).

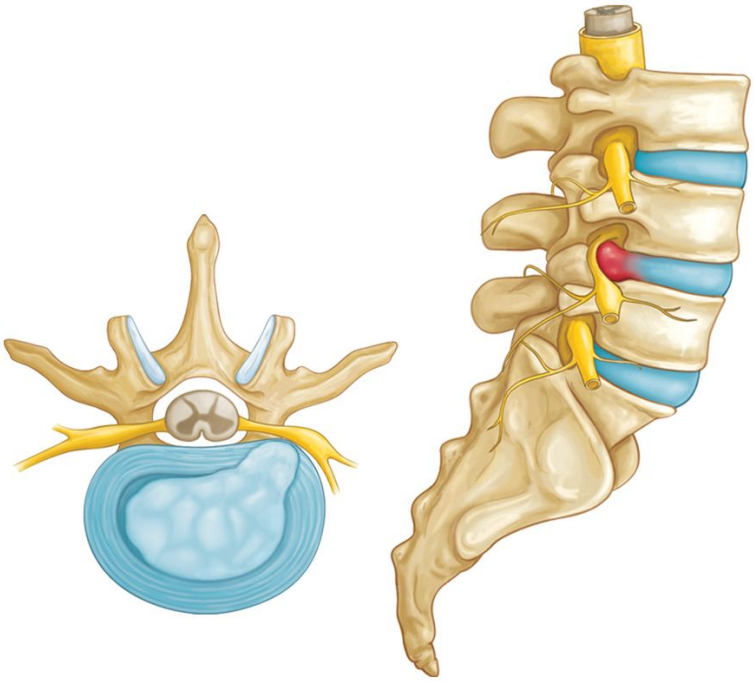

*Figure 3 – Lumbar disc herniation with illustration of nerve-root pressure*
*Reproduced with permission from OrthoInfo © American Academy of Orthopaedic Surgeons. http://orthoinfo.aaos.org.*

## Treatment

The normal clinical course of most LDH is self-limiting, where rest, pain medication and non-surgical management leads to spontaneous regression of symptoms within 6-12 weeks. However, if pain and disability are severe or recovery is unacceptably slow, surgical intervention can provide effective clinical relief (5-7).

The surgical procedure for a LDH is called a discectomy and can be performed with or without visual enhancement in the form of microscope or other source of magnification. The purpose of the procedure is to remove the herniated part of the disc along with any additional fragments that exerts pressure or irritation to the nerve-root (Figure 3).

Literature provides little consensus on the timing of surgery for patients with persistent radicular pain due to LDH. The Danish national clinical guidelines on the topic recommends up to 12

weeks of nonoperative treatment for patients with LDH, as long as they do not present with neurologic deficits or intractable pain (8).

## Outcome

The outcome of discectomy is generally very good, and most patients are able to resume normal activities after a short period of postoperative rehabilitation (9). However, depending on the outcome measure used, 10-40% of patients report unsatisfactory results after lumbar disc surgery (9-11). Due to this relative high number of unsatisfactory operative outcomes, great emphasis should be put on preoperative investigation and diagnostics to find the candidates who will most likely benefit from sugery.

Especially the timing of surgical intervention has been subject to much debate as previous cohort studies have reported inferior results and adverse effects of prolonged preoperative symptoms (12-15). Meanwhile, randomized controlled trials (RCT) report no inferiority in outcome of patients with prolonged symptoms (11, 16, 17). Thus, no studies seem to have found the optimal time window to intervene and perform surgical treatment.

## Pain Perception

Pain is a complex sensory perception affected by biological, psychological and social factors and has a negative impact on most individuals' physical and psychosocial health. Many pain conditions are managed with pain medication that often leads to use and even abuse of opioids. This further burden the healthcare system with chronically afflicted patients and leads to severe cost expenditure for individuals and society (18-20).

Previous studies have found an association between chronic pain conditions and altered sensory perception of pain, leading to different states of hypo- or hyperalgesia (21, 22). There is some evidence that hyperalgesic changes in pain perception develop secondary to chronic pain and normalize following resolution of chronic pain (23). Furthermore, litterature indicates that chronic low-back pain (LBP) may lead to hyperalgesia (24), which in turn adversely affects the efficacy of treatment. Hyperalgesia is a common finding in chronic LBP, but does not constitute a separate risk factor (22, 24-29). These findings suggest that prolonged symptom duration, could lead to altered pain perception and increased clinical pain.

Numerous studies have investigated the predictive value of different preoperative measures to better estimate the clinical outcome a patient can expect from surgical treatment. Many of the factors found to provide predictive value are also related to an individual's chronification or perception of pain. These include psychosocial parameters, financial situation, duration of symptoms, psychological factors, etc.

When assessing pain, an individual's subjective perception has to be quantified on a standardized scale. If such quantifiable measures should be comparable with others, the variation between individuals' perception must be taken into account as pain perception can vary greatly between individuals. Quantitative sensory testing (QST) is group of experimental tests that can be performed to quantify an individual's pain perception or somatosensory profile. QST and somatosensory profiling could potentially be used to asses and perhaps quantify hyperalgesia in such conditions. Previous literature on the predictive value of QST are contradictory and, therefore, more studies are needed to conclude whether these type of measures holds a place in spine surgery.

## Brain Imaging

Modern imaging techniques enable us to assess and even quantify cellular uptake of nutrients, which can then act as a surrogate measure of regional cerebral cell activity in the brain. Such measures are thought to correlate with pain perception and have therefore been suggested as a surrogate measure of quantifiable pain perception.

In a study by Newberg et al. single-photon emission computed tomography was used to analyze cerebral blood flow in patients with chronic pain conditions [4]. Their findings indicated that following acupuncture therapy, cerebral blood flow changed in the frontal lobes and the thalami.

As literature on this subject is sparse, more research is needed; however, brain imaging may have potential as a quantifiable measure to compare pain between individuals and monitor effects of pain therapy.

## Objectives

Founded in previous research the premise is that prolonged duration of preoperative pain can lead to chronification and subsequently altered pain perception. This thesis investigates whether prolonged symptom duration affects surgical outcome in patients with LDH. Furthermore, the predictive value of QST and correlations between 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET/CT) and both clinical outcome and pain perception is evaluated in an attempt to answer the following questions;

- Does prolonged symptom duration cause less favorable outcome following surgery for LDH?
- Is there a correlation between quantitative sensory testing of experimental pain responses and clinical outcome of surgery in LDH patients?
- Is there an association between quantified thalamic glucose uptake assessed by PET/CT and clinical pain perception and outcome in LDH patients?

# Material and Methods

To better clarify the importance of symptom duration and the impact it has on patients with LDH, three separate studies was conducted as part of this thesis.

A retrospective database study (Study I) was performed on patient reported outcome (PRO) measures from the Danish National Spine Registry (DaneSpine) to assess the importance of surgical timing in patients with LDH (Appendix 1 – Manuscript I).

The second study (Study II) was a pilot-study conducted to assess the setup of QST and to evaluate if PET/CT scans were a viable way of identifying pain perception and potentially quantifying it (Appendix 3 – Manuscript III).

The third study (Study III) was designed as a prospective cohort study using QST as a measure of pain perception and subsequently correlating it to relevant clinical parameters (Appendix 2 – Manuscript II).

The two latter studies followed the same protocol with exception of PET/CT as the only change in study III. Study II and III are therefore from this point onwards described and presented as one.

## Study I

### Design

The study was conducted as a retrospective cohort study using prospectively collected patient reported outcomes (PROs) from the Danish National Surgical Spine Database (DaneSpine) (30).

DaneSpine collects pre- and postoperative demographic and clinical data using questionnaires. With the exception of data on surgical indication, type and complications, which is reported by the surgeon, all data is patient reported. Collected parameters include age, sex, height, weight,

preoperative symptom duration, leg and back pain on a 0-100 VAS scale (31), health-related quality of life as measured by the EuroQol-5D (EQ-5D) (32, 33), and spine-related disability as measured by the Oswestry Disability Index (ODI) (34, 35). Surgical data include diagnosis, procedure and complications.

Patients were followed-up with repeat questionnaires one-year post-operative.

Patients with first episode LDH who underwent discectomy at the Spine Center of Southern Denmark from June 1st, 2010 until May 1st, 2017 were included and divided into three groups based on their self-reported duration of leg pain.

Criteria for inclusion and exclusion were as follows.

### Inclusion criteria

- Diagnosed by a senior consultant with LDH (ICD-10 (36); M51.1)
- Underwent discectomy due to LDH
- No cauda equina syndrome or severe neurologic deficits

### Exclusion criteria

- History of previous spine surgery

Prior to their referral to a spine specialist, all patients had received physiotherapy or other relevant exercise therapy via primary care in accordance with the Danish national guidelines for treatment of patients with lumbar disc herniation (37).

## Statistics

Statistics were done as previously described by Stoettrup et al. (38) and repeated here.

All statistical analyses were done using STATA 15 (StataCorp., College Station, TX). Categorical data are presented by frequencies and related percentages; continuous data are displayed by means of descriptive statistics (mean, confidence interval, number of observations). Continuous variables were analyzed for significant difference between the three groups using analysis of variance (ANOVA), categorical variables using Fisher's exact test. Continuous variables found to change orderly across groups were analyzed using a Wilcoxon-type test for trend as developed by Cuzick (1985). Significance level was set at p-value <0.01. Adjustment for potential confounders was done using a forward stepwise regression analysis with an inclusion p-value of 0.10 and a confounding level of 15%.

## Study II and study III

### Design

This experimental study was designed as a prospective cohort study in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (39).

A pilot-study including 20 male and 12 female participants was conducted to assess the setup of QST and to evaluate whether PET/CT scans were a viable way of identifying pain perception and potentially quantifying it. Data was reviewed and evaluated, leading to a modified setup with QST and a dismissal of PET/CT.

Based on the results gained from the pilot-study, it was found reasonable to continue with further study participants in the QST part of the study. Therefore, a continuance of QST measurements was performed on a total of 63 patients, as stated in detail below.

### Study population

Study participants were recruited from consecutive patients assessed and found eligible for LDH surgery at Center for Spine Surgery and Research, Middelfart, part of the Spine Center of Southern Denmark, Lillebaelt Hospital.

Inclusion period for the pilot-study (study II) was between September 2014 and September 2015.

Inclusion period for the subsequent QST supplement study (study III) was between September 2016 and December 2017.

### Inclusion criteria

- Clinical and radiological indication for LDH surgery, assessed by an experienced spine surgeon
- Age 18-70 years (40-70 years for participants included for PET/CT)
- No history of previous spine surgery
- No general contra-indication for spine surgery
- No psychiatric disorders requiring medication within the last 3 months

### Exclusion criteria

- Psychiatric disorder that in the opinion of the investigators could impact the patient's ability to successfully complete the trial or otherwise interfere with outcomes
- Current malignant disease
- Current chemotherapy
- History of spinal fracture
- Hematologic disease
- Current pregnancy or breast-feeding (pregnancy-tested prior to inclusion)
- Chronic, generalized connective tissue disorders or chronic, non-specific pain disorders (fibromyalgia, whiplash (WAD I-V), etc.)
- A competitive clinically significant medical condition that in the opinion of the investigators could impact the patient's ability to successfully complete the trial or otherwise interfere with outcomes

- Has, during the follow-up period, received medication or invasive intervention that in the opinion of the investigators could impact the patient's ability to successfully complete the trial or otherwise interfere with outcomes

### Patient course

Patients identified by the attending surgeon as eligible for were invited to participate. Patients who expressed an interest in participating were given written and oral information on the purpose, nature and implications of study-participation. Information and inclusion of participants was conducted in accordance with the guidelines of The Health Research Ethics Committee System in Denmark (reference S-20140052).

During their primary consultation, participants were examined using a standardized QST battery (described in detail below) in order to assess and quantify their pain sensitivity.

Similarly to study I, demographic and clinical data was collected using questionnaires from DaneSpine and included age, sex, height, weight, preoperative symptom duration, leg and back pain on a 0-100 VAS scale (31), health-related quality of life as measured by the EuroQol-5D (EQ-5D) (32, 33) and Short Form 36 Health Survey (SF-36) (40, 41), and spine-related disability as measured by the Oswestry Disability Index (ODI) (34, 35). Questionnaires were repeated one-year post-operative.

All participants underwent standard operative treatment with discectomy by a senior consultant employed at the facility. The preoperative examination, assessment and subsequent treatment offered were not affected by study participation.

## Quantitative Sensory Testing

The standardized QST battery was constructed as a compromise of feasibility and comprehensiveness based on previous literature and in collaboration with supervisor Søren O'Neill who has experience in the field of pain research. In order to incorporate different modalities of pain perception and pain stimuli, the QST battery consist of 3 different test types; mechanical, thermal and chemical stimulation (Table 1). The following is also described in the manuscript on preoperative QST in patients with LDH (Appendix 2).

*Table 1 - Overview of which variables were tested using which test modality*

| | Pain Detection Threshold | Pain Tolerance Threshold | Pain Response | Continuous Pain Response | Complex Pain Modulation |
|---|---|---|---|---|---|
| Mechanical | PPDT | | PPDT | | PPDT |
| Thermic | | CPT | | CPT | CPT |
| Chemical | | | NaCl | NaCl | |

Initially participants underwent a simple Pressure Pain Detection Threshold test (PPDT) using a handheld electronic pressure algometer (Somedic, Hörby, Sweden) at the thenar eminence of the hand and the most painful site of the lumbar area (Figure 4). Pressure was applied at a rate of 30 kPa/s using a 1 $cm^2$ probe. Participants were instructed to indicate when the applied pressure was perceived as just becoming painful, by pressing a button attached to the algometer. Two consecutive measurements were performed, and the mean value was defined as the Pressure Pain Detection Threshold.


*Figure 4 – Electronic Pressure Algometer by Somedic SenseLab*
*Reproduced with permission from Somedic SenseLab AB. http://somedic.com.*

Pain intensity at 140% of the individual PPDT was subsequently rated on a visual analog scale from 0-100 (VAS) and recorded as the Pain Response (PR) (42).

Next, participants underwent a Cold-Pressor Test (CPT) using a container of refrigerated water (0-2°C) in which they were asked to submerge their non-dominant hand to the wrist for 2 minutes. During the CPT, pain response was monitored using an electronic continuous VAS (1 Hz) as it developed over time. For individuals who failed to tolerate the entire 2 minutes, time of withdrawal was recorded, and pain intensity was considered to be maximal for the remainder of the 2 minutes. Immediately following the CPT, participants were, once again, tested using the PPDT and PR test described above. This repetition was performed to assess Conditioned Pain Modulation (CPM) in the central nervous system.

Finally, after a break of approx. 3-5 min., participants received an injection of 1 mL sterile hypertonic saline (58.5 mg/mL) at the infraspinatus muscle of the scapula. Once again, pain response was measured as it developed over time using a continuous VAS (0-100).

Participants where dichotomized into two distinct somatosensory profiles (SSP); normal and altered, based on their QST results. Using reference data, Magerl et al. (43) for PPDT and Neziri et al. (44) for CPT, an altered QST profile for PPDT was defined as a Z-score of minus two or less; for CPT it was defined as a withdrawal time below the 5$^{th}$ percentile and/or area under the curve (AUC) above the 95$^{th}$ percentile. All reference data comparisons were age and gender matched. Altered SSP was defined as two or more altered QST results.

### PET/CT Imaging

The acquisition of PET/CT images were performed at the Department of Nuclear Medicine, Odense University Hospital, in accordance with local standard operating procedures. The below mentioned procedure has been described in the manuscript for study II (Appendix 3).

Participants were asked to refrain from pain medication 36 hours (5 x the half-life of relevant drugs) prior to their PET/CT scan and were kept fasting for at least 6 hours before their scan. They were placed supine on the tomography bed in a quiet room with dim lighting and their head was immobilized with a dedicated headrest. Following 10 minutes of rest, FDG (4 MBq/kg body weight) was administered intravenously. Images were obtained using an acquisition protocol with 47 slices (3.3 mm) in each frame on a General Electric Discovery PET/CT 690 or 710 scanner. A complete PET/CT scan from the top of the head to the sacrum was performed and the data from 60-90 minutes was summed and used for analyses.

PET images were segmented and analyzed using ROVER software (v2.1 ABX, Radeberg, Germany) (Figure 5). Proper head alignment was examined prior to defining region of interest (ROI). Head tilt was corrected manually on the CT using a global pixel shift, thereby not altering pixel size or values. After fusing the PET/CT using DICOM information, a rigid correction for head movement on the PET image was done in order to ensure proper PET/CT overlap. Subsequently, an ovoid ROI was defined by the observer on a scan-to-scan basis to best fit the thalamus structure in one hemisphere. This mask was then duplicated in exact size and shape and applied to circumscribe the contralateral thalamus.

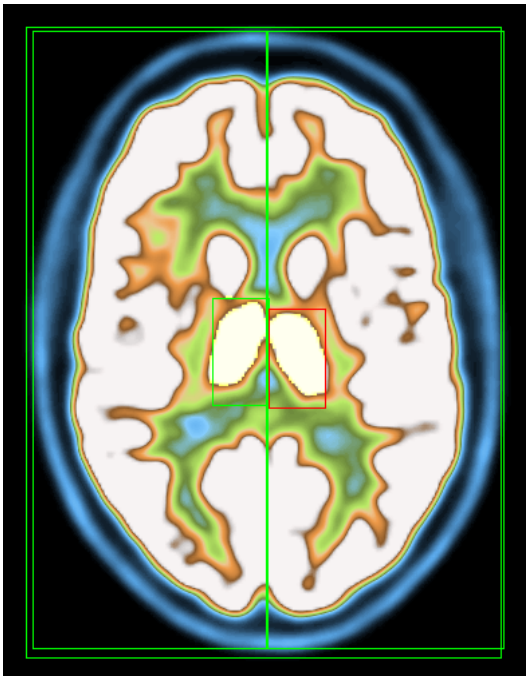

*Figure 5 – Example of PET/CT scan as presented in ROVER*

A lower fixed threshold of 41% of the peak standardized uptake value (SUV) was applied to exclude cerebrospinal fluid activity and the spillover from other surrounding structures in accordance with European Association of Nuclear Medicine guidelines (45). For each of the segmented regions, ROVER calculated the volume of the ROI together with the following range of SUV metrics: maximum, mean, mean partial volume corrected, which were designated SUVmax, SUVmean, cSUVmean, respectively.

Prior to further analysis of PET/CT data, all participants were tested for hemispheric diaschisis in order to eliminate any generalized cerebral metabolic lateralization. In brief, diaschisis is the finding of a remote functional disturbance in a region connectively related to a focal brain damage area. The presence of diaschisis is searched for by calculating the total hemispheric glucose metabolism ratio (THGr) as described by Segtnan et al. (46).

For each SUV metric (max, mean and partial volume corrected mean), the hemisphere with the highest thalamic SUV measure was entered into a contingency table and compared to the side of radicular leg pain as registered using the baseline questionnaire.

A mean thalamic glucose metabolism ratio (MTGr) was computed by indexing the cSUVmean of the thalamus contralateral to the pain side against the ipsilateral thalamic metabolism. The resulting MTGr values indicated the hypothesized relation between metabolism lateralization and pain side when values were above one.

### Sample size rationale

Sample sizes for the pilot-study were chosen using collaborated knowledge on sample size rationales from all the supervisors involved in the project.

Based on the data gathered during the initial pilot-study, reverse power-calculations have been performed in order to provide sufficient data for statistical significance in the supplemental QST study. Based on these calculations an estimated study group of 70-100 participants should yield statistical significance.

### Statistics

All statistical analyses were performed with STATA 16 (StataCorp., College Station, TX). A p-value of $<0.05$ was considered significant. All QST data were visually inspected for normal distribution using normal quantile plots and statistically tested using Shapiro-Wilk test for normality. If data were found to have a non-normal distribution, data were log10 transformed prior to further analysis.

Categorical data are summarized as frequencies and related percentages; continuous data are summarized as mean/median, standard deviation, and number of observations. Categorical

variables and contingency tables on PET data were analyzed for significant difference using Fisher's exact test. Continuous variables on clinical parameters were analyzed for correlations with PET/CT parameters using Spearman's rank correlation coefficient test. Correlation coefficients of <0.40 were considered weak.

Continuous variables on QST data were analyzed for significant between-group differences for the two SSP groups using student's t-test, categorical variables using Fisher's exact test.

All clinical outcome parameters (EQ5D, ODI, VAS and SF-36) were assessed for correlation with QSTs using Spearman's rank correlation coefficient test and linear regression analysis.

## Regulatory compliance

The study has been registered with the Regional Committees on Health Research Ethics for Southern Denmark and the Danish Data Protection Agency.

All patient data, including sensitive personal information, are strictly confidential and stored according to the Danish Open Administration Act, the Health Act, the Danish Act on Processing of Personal Data and the later Danish Act on Data Protection (GDPR).

## Ethics

The current clinical trial was conducted in accordance with both the Danish ethical principles and the Declaration of Helsinki.

### *Patient rights*

Patients' rights were taken into account, as participation in the study was completely voluntary and only took place after receiving both oral and written information about the study.

The participants were entitled to bring a member of the family or a friend to the informative interview and were given ample time to consider participation before signing a consent form. The Informed Consent form was signed by all participating patients and stored at the Center for Spine Surgery and Research, Middelfart.

In Accordance with the Danish Open Administration Act the participants were entitled to review the research protocols and documents concerning the patient's own participation in the study.

### *Subject withdrawal*

At any time during the study, the participants could withdraw their consent orally, in writing or by any other clear notification. If the participant chose to withdraw their consent it did not affect their right to any current or future treatment. Participants could opt to withdraw consent to all data collected during the study, or opt-out of any further participation, but let the already collected data remain available to the investigators.

### *Irradiation*

In each patient a PET/CT scan with low dose CT (without contrast enhancement) was performed on three occasions, i.e. at baseline, 6 weeks and 6 months postoperative. According to recent literature and department instructions (Department of Nuclear Medicine, OUH), the participants received 18-19.5 mSv, on average, from the three occasions they were scanned (Table 2) (47, 48):

*Table 2 - Approximate doses of radiation exposure during participation*

| | | | |
|---|---|---|---|
| *A. 3 x PET with FDG* | *= approx.* | *12-13.5* | *mSv* |
| *B. 3 x CT for the correction of the above* | *= approx.* | *6* | *mSv* |
| *Total* | *= approx.* | *18-19.5* | *mSv* |

This makes the project a Category III research project according to the classification by the European Commission and the International Commission on Radiation Protection (ICRP) (49). Category III projects are such that imply doses in the range >10 mSv to 25-year old adults in whom the estimated added risk of dying of cancer due to this irradiation is considered larger than one in 1,000, equivalent to an increased risk of 0,1%.

To justify a research project in this category, the degree of benefit to society should be "considerable and related to protection of life or prevention or mitigating of serious disease" (49). The potential clinical relevance of identifying patients with LDH who will not benefit from surgery would in a combined socio-economical perspective save both society and the individual patient. Furthermore, diagnosing and grading pain sensitization quantitatively would be novel and undoubtedly generate large numbers of further studies with a vast clinical potential. For these reasons the radiation doses used in this study were found to be justifiable.

The above-mentioned risks are theoretical estimates for the additional risk of dying from cancer, which can be added to the risk of approximately 25% that 25-year-old adults already have to die of cancer at some time point later in life. With age, this theoretical risk decreases, meaning that on average, the risk of persons aged 60 years or more, is 5-10 times less. Thus, the effects of the doses received by our participants, all of whom are above 40 years of age, is of less importance and therefore the study might be regarded as a Category IIb research project.

# Results

## Study I

A total of 2,586 patients were surgically treated for radicular pain due to LDH at the Spine Center of Southern Denmark during the inclusion period. Four hundred forty-two (17.1%) were excluded from further analysis due to previous spine surgery, leaving 2,144, of which one-year follow-up data was available for 79%. Almost 80% (1,708) of patients underwent surgery within one year from onset of radicular leg pain. Patients were divided into 3 groups as previously described and baseline demographics and preoperative PROs are displayed in Table 3.

Mean age was 46.8 years with minor differences between groups. Gender distribution were 54.4% males in the entire cohort, with a higher distribution of males in the <3-months duration group. The prevalence of smoking was 32.7% with a tendency of increased prevalence with longer duration of leg pain. Baseline EQ-5D and ODI were significantly worse with shorter duration of preoperative leg pain. The opposite was the case with back pain, which was found to be worse with longer duration of symptoms. None of these differences, however statistically significant, were clinically relevant.

*Table 3 - Baseline characteristics of cohort and subgroups*

| | All (*n* = 2.144) | <3 months (*n* = 613) | 3-12 months (*n* = 1.095) | >12 months (*n* = 436) | *p*- value of difference |
|---|---|---|---|---|---|
| Age, mean (95 % CI) | 46.8 (46.2 ; 47.4) | 48.1 (47.1 ; 49.2) | 46.7 (45.8 ; 47.5) | 45.2 (43.8 ; 46.6) | 0.003 |
| Males, *n* (%) | 1.167 (54.4) | 366 (59.7) | 572 (52.2) | 229 (52.5) | 0.008 |
| Smokers, *n* (%) | 699 (32.7) | 173 (28.3) | 369 (33.8) | 157 (36.2) | 0.015 |
| EQ-5D baseline, mean (95% CI) | 0.45 [0.44;0.46] | 0.39 [0.37;0.42] | 0.47 [0.45;0.48] | 0.48 [0.45;0.50] | <0.001 |
| ODI baseline, mean (95% CI) | 47.76 [46.97;48.55] | 52.14 [50.47;53.80] | 46.55 [45.54;47.56] | 44.69 [43.05;46.32] | <0.001 |
| VAS leg baseline, mean (95% CI) | 67.76 [66.74;68.78] | 67.92 [65.85;69.99] | 67.94 [66.58;69.29] | 67.10 [64.87;69.33] | 0.138 |
| VAS back baseline, mean (95% CI) | 48.10 [46.86;49.34] | 43.75 [41.39;46.12] | 48.82 [47.11;50.52] | 52.41 [49.69;55.12] | <0.001 |

A total of 179 (8.4%) cases of reoperation within one year of primary surgery were registered. The primary surgical intervention was repeat discectomy with the remaining divided between additional decompression, removal of hematoma, drainage of infection and other non-specified surgical intervention. An increasing incidence of reoperation was found with increasing length of preoperative symptom duration (*p*-value 0.008). A detailed overview can be found in Appendix 1 (38).

One-year postoperative PROs are presented in Table 4 with significant improvements across all groups compared to baseline measures. Patients with symptom duration less than one year had better one-year outcome across all four PRO parameters. The same was found in VAS leg pain change score, whereas both EQ-5D and ODI change scores from baseline to one-year follow-up were found to increase with shorter duration (Figure 6).

*Table 4 - One-year PRO measures follow-up*

| | All (n = 2.144) | <3 months (n = 613) | 3-12 months (n = 1.095) | >12 months (n = 436) | *p*- value of trend |
|---|---|---|---|---|---|
| EQ-5D; mean (95% CI) | | | | | |
| *Post-operative* | 0.77 [0.76;0.78] | 0.78 [0.76;0.80] | 0.77 [0.76;0.79] | 0.72 [0.70;0.75] | 0.001 |
| *Change from baseline* | 0.31 [0.30;0.33] | 0.39 [0.35;0.42] | 0.30 [0.28;0.32] | 0.24 [0.20;0.27] | <0.001 |
| ODI; mean (95% CI) | | | | | |
| *Post-operative* | 20.91 [20.05;21.77] | 19.36 [17.86;20.86] | 20.50 [19.31;21.69] | 24.25 [22.20;26.31] | 0.001 |
| *Change from baseline* | 26.72 [25.62;27.83] | 32.87 [30.71;35.03] | 25.96 [24.49;27.43] | 19.68 [17.41;21.94] | <0.001 |
| VAS leg; mean (95% CI) | | | | | |
| *Post-operative* | 24.39 [23.07;25.72] | 23.05 [20.72;25.37] | 22.51 [20.72;24.30] | 31.51 [28.17;34.85] | 0.001 |
| *Change from baseline* | 43.16 [41.53;44.80] | 44.92 [41.86;47.99] | 45.10 [42.87;47.34] | 35.21 [31.51;38.91] | <0.001 |
| VAS back; mean (95% CI) | | | | | |
| *Post-operative* | 26.89 [25.59;28.19] | 23.88 [21.67;26.10] | 25.99 [24.21;27.78] | 34.03 [30.73;37.32] | <0.001 |
| *Change from baseline* | 20.12 [18.57;21.68] | 19.88 [17.00;22.77] | 21.32 [19.13;23.52] | 17.23 [13.83;20.62] | 0.436 |

To adjust for potential confounders, statistical analyses were performed using age, gender, BMI, smoking status, duration of back pain and social welfare status in a model as previously described (Material and Methods; Study I – Statistics). Age and BMI did not reach significance level

or confounding level above the set limits. Duration of back pain had an inverse effect on PROs ($p$ = 0.022) and receiving social welfare was found with a positive correlation to outcome ($p$ <0.001).

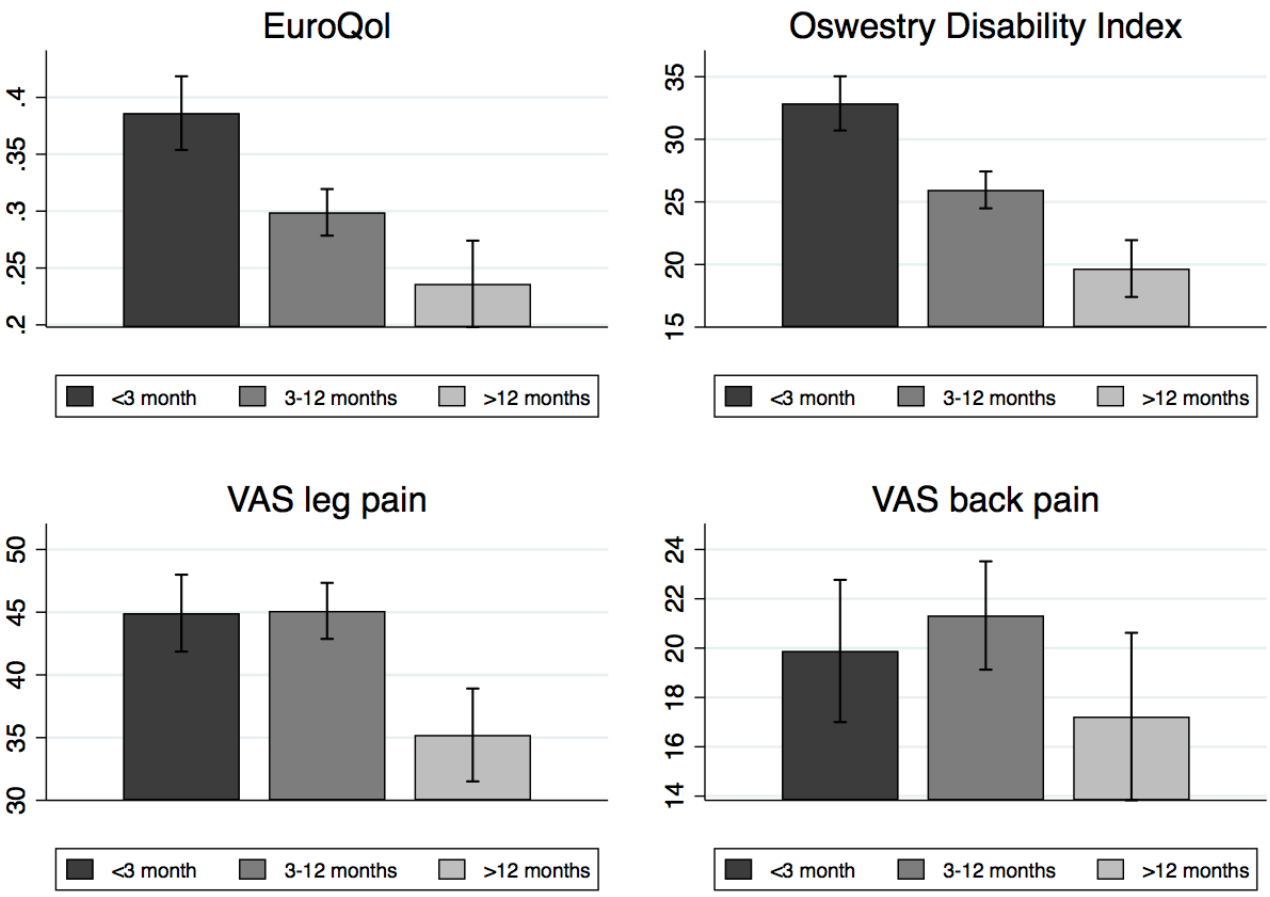


*Figure 6 - Change in patient-reported outcomes (PROs) at one-year follow-up (mean;CI)*[1]

[1] *Reprinted from "Increasing reoperation rates and inferior outcome with prolonged symptom duration in lumbar disc herniation surgery - A prospective cohort study" by* Stottrup CC, Andresen AK, Carreon L, Andersen MO*,* 2019*,* The Spine Journal: official journal of the North American Spine Society*, 19, 1463-69. Reprinted with permission.*

## Study II and III

During the two inclusion periods, pilot and supplemental, a total of 63 participants were included, of which 32 were during the pilot phase and therefore part of the PET/CT protocol. One patient experienced spontaneous symptom relief and, thus, excluded from further analyses. For various reasons, baseline PET/CT scans were not performed on 5 of the 32 included participants, leaving 26 participants with PET/CT scans and 62 with preoperative QST measurements. Follow-up rate at one-year was 79% across the cohort.

Mean age was 46.8 years with 53.2% males and 15.9% had experienced preoperative symptoms for more than one year. The PET/CT cohort had a slightly higher mean age and a gender distribution with male majority. No significant differences were found in the remaining baseline characteristics (Table 5).

*Table 5 - Baseline characteristics of respective cohorts*

| | All (*n* = 62) | PET/CT protocol (*n* = 26) |
|---|---|---|
| Age, mean (SD) | 46.8 (11.4) | 49.7 (7.35) |
| Males, *n* (%) | 33 (53.2) | 16 (61.5) |
| BMI, mean (SD) | 25.6 (3.35) | 26.3 (3.72) |
| Duration of legpain >1 year, *n* (%) | 10 (15.9) | 4 (15.4) |
| EQ5D baseline, mean (SD) | 0.53 (0.23) | 0.53 (0.21) |
| ODI baseline, mean (SD) | 41 (15.3) | 42.9 (12.7) |
| VAS leg baseline, mean (SD) | 64.3 (19.7) | 65.3 (20.6) |
| VAS back baseline, mean (SD) | 42.5 (27.9) | 39.5 (26.2) |

## QST data

The QST results of participants were compared with reference data and categorized as normal or hypersensitive response as illustrated in Table 6. Of the 62 participants, 8 had two or more hypersensitive responses and were categorized as having an altered somatosensory profile.

*Table 6 - Distribution of participants' QST results relative to reference data*

| | Normal response | Hypersensitive response |
|---|---|---|
| PPDT thenar, *n* (%) | 62 (100) | 0 (0) |
| PPDT lumbar, *n* (%) | 52 (83.9) | 10 (16.1) |
| CPT withdrawal-time, *n* (%) | 54 (87.1) | 8 (12.9) |
| CPT VAS area-under-curve (AUC), *n* (%) | 51 (82.3) | 11 (17.7) |
| Two or more hypersensitive responses, *n* (%) | 54 (87.1) | 8 (12.9) |

Baseline demographics were similar across the two SSP groups with no statistically significant difference for age, smoking status, BMI or preoperative duration of leg pain. Though not statistically significant, the altered SSP group had a higher proportion of females with 75% relative to 42.6% in the normal SSP group. Patient reported outcome measures at baseline and at one-year follow-up were similar between the two groups (Table 7). No statistical difference was found for any of the outcome parameters.

*Table 7 - Changes in patient-reported outcomes at one-year follow-up*[2]

| | All ($n$ = 62) | Normal SSP ($n$ = 54) | Altered SSP ($n$ = 8) | $p$-value of difference |
|---|---|---|---|---|
| EQ-5D; mean (SD) | | | | |
| *Pre-operative* | 0.53 (0.23) | 0.54 (0.22) | 0.50 (0.30) | 0.657 |
| *Post-operative* | 0.86 (0.14) | 0.86 (0.14) | 0.85 (0.13) | 0.936 |
| *Difference* | 0.32 (0.24) | 0.32 (0.24) | 0.22 (0.24) | 0.503 |
| ODI; mean (SD) | | | | |
| *Pre-operative* | 41.0 (15.3) | 40.5 (14.8) | 44.0 (19.1) | 0.557 |
| *Post-operative* | 11.6 (9.52) | 11.7 (10.1) | 10.4 (2.97) | 0.770 |
| *Difference* | 28.9 (15.2) | 29.4 (15.4) | 25.2 (14.4) | 0.571 |
| VAS leg; mean (SD) | | | | |
| *Pre-operative* | 64.3 (19.7) | 64.3 (19.4) | 63.9 (23.0) | 0.952 |
| *Post-operative* | 8.29 (12.2) | 8.81 (12.7) | 3.80 (4.76) | 0.390 |
| *Difference* | 52.4 (18.6) | 52.8 (18.6) | 49.6 (20.6) | 0.723 |
| VAS back; mean (SD) | | | | |
| *Pre-operative* | 42.5 (27.9) | 43.7 (27.5) | 34.5 (31.7) | 0.387 |
| *Post-operative* | 14.0 (20.9) | 12.6 (18.1) | 26.2 (39.2) | 0.172 |
| *Difference* | 26.1 (27.8) | 27.5 (26.6) | 13.8 (37.8) | 0.303 |
| SF-36 PCS; mean (SD) | | | | |
| *Pre-operative* | 32.1 (7.13) | 31.8 (7.38) | 34.1 (5.01) | 0.386 |
| *Post-operative* | 48.1 (8.68) | 48.2 (9.08) | 47.0 (4.06) | 0.766 |
| *Difference* | 16.0 (8.53) | 16.6 (8.43) | 10.6 (8.26) | 0.139 |
| SF-36 MCS; mean (SD) | | | | |
| *Pre-operative* | 46.3 (9.94) | 46.1 (10.0) | 47.4 (9.90) | 0.746 |
| *Post-operative* | 55.0 (8.58) | 54.6 (8.86) | 58.2 (5.08) | 0.382 |
| *Difference* | 8.87 (11.0) | 8.71 (11.0) | 10.3 (11.8) | 0.764 |

QST results were evaluated for correlation with clinical parameters at baseline and one-year follow-up using Spearman's rank correlation coefficient test. Although some coefficients reached statistical significance, none reached a level of even moderate strength ($\rho$>0.40) and therefore not considered of any clinical relevance.

[2] Discrepancies in change scores are due to the incomplete follow-up on post-operative data

Linear regression models showed similar results, with p-values below significance level and beta values of little clinical relevance. Complete description and presentation of regression analysis results can be found in Appendix 2.

### PET/CT data

In accordance with previous literature the entire PET/CT material was tested for cerebral diaschisis with the following values of THGr: mean 0.96, median 0.98, range 0.89-1.00. No outliers were identified, and values indicate normal conditions according to previous literature (46, 50).

To test the hypothesis of lateralization of thalamic metabolism in conjunction with unilateral pain, contingency tables were evaluated (Table 8). Baseline PET/CT scans were available for 26 participants, however, one participant reported bilateral radicular leg pain and was therefore not included in these analyses.

*Table 8 - Comparison of painful body side and increased PET/CT activity in the thalamus*

| | Painful body side | | |
|---|---|---|---|
| Increased PET/CT activity | Right | Left | *p* -value |
| **SUVmax**, *n=25* | | | |
| Right, *n* (%) | 5 (20%) | 4 (16%) | |
| Left, *n* (%) | 6 (24%) | 10 (40%) | 0.325 |
| **SUVmean**, *n* =25 | | | |
| Right, *n* (%) | 4 (16%) | 9 (36%) | |
| Left, *n* (%) | 7 (28%) | 5 (20%) | 0.163 |
| **cSUVmean**, *n* =25 | | | |
| Right, *n* (%) | 2 (8%) | 9 (36%) | |
| Left, *n* (%) | 9 (36%) | 5 (20%) | 0.027* |

As presented in Table 8, both SUVmean and cSUVmean indicated lateralization towards the thalamus of the hemisphere contralateral to the registered side of radicular pain. No clear pattern

was found for SUVmax. Statistical significance was found for cSUVmean (*p*-value 0.027) using one-sided Fisher's exact test.

To investigate whether PET/CT scan metrics correlated with clinical parameters, the computed MTGr was evaluated for correlations with patients' reported pain perception and subsequent clinical outcome measures. Correlation coefficients for baseline PROs (EQ-5D, ODI, SF-36, VAS leg and back) and MTGr were generally low ($\rho$<0.40) and none reached statistical significance.

A separate correlation analysis was run using the 18 patients that followed the hypothesis of an increase in thalamic glucose metabolism contralateral to the painful body region (Table 8). A correlation coefficient of -0.47 (*p*-value 0.048) was found for EQ-5D and MTGr. The remaining coefficients indicated weak correlations.

To examine if MTGr values were associated with one-year clinical outcome, similar correlation analyses were run using one-year change scores of PROs. The Spearman's rank correlation coefficient with EQ-5D change score was 0.54, but statistically non-significant (*p*-value 0.167). Furthermore, the coefficient between MTGr and change in VAS leg pain was -0.51 (*p*-value 0.194). Once more, the remaining coefficients were weak and non-significant.

# Discussion

Study I found self-reported outcomes to be worse in patients with preoperative duration of leg pain of more than three months.

Study II found no significant difference in preoperative demographic, clinical data or the PRO measures one-year postoperative when stratified in two groups based on somatosensory profiling.

Study III found a pattern of increased glucose metabolism in the thalamus contralateral to the painful body region. Furthermore, there was a moderate correlation between both preoperative and one-year postoperative quality of life data and the ratio of glucose metabolism in the thalamus.

The efficacy of discectomy as treatment of LDH is hard to dispute. The results presented in the present thesis as well as previous literature finds discectomy to be an effective treatment regardless of symptom duration (5, 7, 9-17, 51, 52).

The study population of this thesis consisted of patients in their forties with a slight overweight of males, a higher prevalence of smokers and with leg pain as their primary complaint. In general, the study population seems comparable to that of earlier studies on both demographics and preoperative parameters (11, 17, 52).

## Duration of symptoms

In accordance with previous literature, study I found significantly and clinically relevant improvement across all four outcome parameters (EQ-5D, ODI, VAS leg- and back pain). However, as shown in both Table 4 and Figure 6 these improvements are adversely affected if the duration of preoperative symptoms is more than one year. Nygaard et al. have previously published similar results, where surgical outcome was found more favorable in patients with less than 6 months

preoperative symptom duration (13). A cohort study by the same lead author found less favorable outcome in patients with more than 8 months of preoperative leg pain (12).

Pitsika et al. found a trend of decreased efficacy of surgery, as measured by change in ODI, with increasing duration of preoperative symptoms (14). A large cohort study, based on the SPORT cohort, found prolonged duration of preoperative symptoms to have adverse effects on outcome in both surgically and non-operatively treated patients (15).

The causal reason for prolonged duration of leg pain to cause inferior outcome may include both psychological and physiological explanations. Prolonged sick-leave and subsequently a lower chance of return-to-work postoperatively may be a consequence of prolonged symptom duration (53). The delay in return-to-work may cause a negative psychological effect, as well-being and the feeling of purposeful living are affected by the ability to "serve society".

The physiological explanation is more extensive and could include both inflammatory processes, the ability of tissue to repair/regenerate, and the brain's modulation of pain perception.

A disc herniation may cause a large immunological inflammatory response similar to that caused by surgery. If such an inflammatory response persists for a prolonged duration of time, it may negatively affect the surrounding tissue and its ability to remodel/recover, even if the herniation has been removed.

The perception of pain is subjective, and our knowledge of the brain's reception, modulation and translation of pain stimuli from the peripheral system is limited. Literature reports that chronic pain conditions lead to an altered response to QST (21-23), and one might speculate if a prolonged pain stimulus, e.g., a persistent disc herniation, may change the brain's modulation of pain and thereby alter the conscious perception of pain.

## Quantitative Sensory Testing

Quantitative sensory testing and subsequent somatosensory profiling have previously been found effective in identification of generalized hyperalgesia and hypersensitivity to experimental stimuli (21, 23, 25, 26).

The findings presented in Table 7 suggest no difference in demographics or outcomes between the two SSPs stratified by the QST results. This is in line with previous literature that reports little evidence on association between QST and postoperative outcome of spine surgery (54-56). However, two studies by Lindbäck et al. have reported significant associations between QST, SSP, baseline demographics and outcome parameters (57, 58). These contradictory results may be explained by differences in the cohorts, as the proportion of patients with prolonged (>2 years) duration of preoperative leg pain was significantly higher in the study by Lindbäck et al. Furthermore, both VAS leg and back was higher in their cohort, and, thus, constitute baseline demographic differences between the cohorts.

Participants in study I have both more favorable baseline PROs and significantly superior one-year outcomes when compared with participants in study II and III. These discrepancies in outcome measures might be a result of differences in preoperative duration of pain and may very well constitute a further explanation of the deviation of our findings compared to those reported by Lindbäck et al.

Thus, QST may or may not be used to predict clinical outcome in spine surgery, but both previous and present findings suggest that the clinical usefulness of such tests is most likely very limited.

## Brain Imaging

The use of cerebral imaging in assessment of pain perception is still a very novel field and only few previous studies have been published. Thus, no standardized protocol for using PET/CT to quantify changes in brain metabolism as a result of painful stimuli exists. The methods applied in this thesis have been composed with foundation in the European Association of Nuclear Medicine procedure guidelines for tumor imaging (45). By applying known methods for quantification of metabolism we sought to facilitate transparency and easier reproduction.

The relation between thalamic metabolism and unilateral pain presented in Table 8 is supported by the few previous results published in this novel field. Newberg et al. has previously found significant asymmetry in thalamic blood flow using single-photon emission computed tomography (59). Their findings indicated a significantly higher degree of lateralization in patients with pain compared to healthy controls. Similarly, Guillot et al. has published findings of significantly increased thalamic activity in cats with osteoarthritis-associated pain (60).

As previously mentioned, all our scans were individually tested for cerebral diaschisis as described by Segtnan et al. (46, 50). All values were within normal limits of healthy individuals and, thus, any preexisting hemispheric imbalance could be ruled out.

Results on SUVmax presented in Table 8 indicate no pattern of lateralization between thalamic activity and the side of radicular leg pain. Lateralization of thalamic metabolism was hypothesized as afferent synapses in the thalamus would be more active with increased stimuli, i.e., radicular leg pain. Thus, SUVmax would not necessarily be increased as the synapses in question might be relatively scattered in the thalamus. On the contrary, both SUVmean and cSUVmean should provide a more reliable measure of overall activity in the thalamus and the presented pattern of increased glucose metabolism of the thalamus contralateral to the registered side of radicular pain was

therefore anticipated. The higher statistical significance of the partial volume corrected measure (cSUVmean) may be due to the relatively small volume of the thalamus and consequent higher influence of the correction for partial volume effect (61). Furthermore, by using the ratio between the two hemispheres, each patient serves as his or her own control, thereby adjusting for any inter-scan differences, which otherwise might affect the results.

The reported correlations between glucose metabolism and EQ-5D yielded moderate coefficients with borderline or insignificant statistics. No correlations were found with other clinical parameters such as VAS or perceived disability (ODI). Scatterplots did not indicate a convincing pattern (data not shown), which leads to speculations on whether correlations actually exist. The reported coefficients for EQ-5D indicated worse quality-of-life at baseline and greater change-scores at one-year follow-up with increased thalamic imbalance. This is in line with the hypothesis that increased imbalance of thalamic activity is indicative of decreased physical and psychological well-being, i.e., chronic pain condition.

## Limitations

### Study I

Being a database study, the retrospective analysis and lack of complete follow-up are the major drawbacks of study I. As all data in DaneSpine are collected prospectively and the study included more than 2,000 consecutive patients, the potential bias or systematic errors introduced by these limitations are most likely negligible. Furthermore, a previously published drop-out analysis on part of the same cohort found non-responders to be primarily males younger than the average cohort population and with better outcomes across PRO parameters (30).

As previous literature has suggested the “golden cut-off” time point to be somewhere around six months it would have been superior with a continuous registration of the primary variable of interest in study I (duration of preoperative leg pain) as compared to the categorical registration used. This is one of the limitations that come with the use of a database, however, in order to better estimate the “optimal time-point” of surgical intervention, future studies should aspire to collect duration as a continuous variable.

### Study II and III

Although the largest to date, our relatively small cohort may give rise to larger standard deviations and subsequently lead to greater chance of type II errors, as even few outliers will have relatively larger impact on results.

Participants’ use of pain medication is a limitation of unknown proportions, as many participants were using pain medication during their initial QST, performed on the day they were found eligible for surgery. Despite participants being asked to refrain from pain medication up to the day of their PET/CT, the actual compliance is unknown.

Outcome measures at one-year follow-up presented for the cohort indicate superiority on many parameters compared with equivalent cohorts. This may be a coincidence but may also be the result of study inclusion and subsequent additional attention and follow-up.

The applied method of quantification of metabolism in the thalamus is experimental and non-standardized, although general guidelines were sought applied. As a result, quantitative measures are probably somewhat observer dependent.

## Conclusion

In patients with lumbar disc herniation persistent to non-surgical care, duration of radicular leg pain prior to surgical intervention adversely affects clinical outcome at one-year follow-up. When tested with QST some will have responses outside of reference intervals, however, no correlation was found between such hypersensitive responses and clinical outcome measures. Though associations between hypersensitive QST results and clinical measures cannot be outright rejected, the clinical usefulness of such tests appear to be limited in a spine surgery setting.

The use of PET/CT as a quantitative measure of pain perception in a clinical setup is not viable, however, in line with previous literature, our findings suggest that thalamic metabolism may increase in the hemisphere contralateral to radicular leg pain in patients with LDH.

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## Appendix 1 – Manuscript I

# Increasing reoperation rates and inferior outcome with prolonged symptom duration in lumbar disc herniation surgery- A prospective cohort study

*Christian C. Støttrup[1,2] • Andreas K. Andresen[1,2] • Leah Carreon[1,2] • Mikkel Ø. Andersen[1,2]*

[1]Spine Center of Southern Denmark – Lillebaelt Hospital, Middelfart, Denmark

[2]Department of Regional Health Research – University of Southern Denmark, Odense Denmark

**Corresponding author:**

Christian C. Støttrup, MD

Spine Center of Southern Denmark – Lillebaelt Hospital, Middelfart, Denmark

Email: Christian.Stottrup@rsyd.dk

Phone: +45 2966 0602

**Background Context:** Lumbar disc herniation (LDH) is associated with great morbidity and significant socioeconomic impact in many parts of the world. Studies have shown that most LDH can be treated effectively with nonoperative management. However, for some patients in whom pain and disability are unacceptable, surgical intervention provides effective clinical relief. Currently there is little consensus in the medical community on the timing of surgery for patients suffering from radicular pain due to LDH. Multiple studies suggest that prolonged symptom duration adversely affects clinical outcome.

**Purpose:** The aim of this study is to evaluate if prolonged symptom duration is correlated with less favorable outcome following surgery for LDH.

**Study Design/Setting:** Consecutive series of patients from a single-center, multi-surgeon, tertiary spine practice.

**Patient Sample:** Consecutive series of patients who underwent surgery for lumbar disc herniation.

**Outcome Measures:** Oswestry Disability Index (ODI), EuroQol-5D (EQ-5D) and Visual Analog Scale (VAS) for back and leg pain (0 to 100).

**Methods:** Patients with a first episode LDH were included. Data were prospectively collected in DaneSpine, the Danish National Spine Registry. Subjects were divided into three groups based on their preoperative self-reported duration of leg pain: <3-months, 3-12 months and >12-months. Associations between patient-reported outcomes (PROs), perioperative complications and duration of symptoms were evaluated. Statistical significance level was set at p-value <0.01.

**Results:** There were 2,144 patients included in the study, with complete one-year follow-up on 1,694 patients (79%) and a reoperation rate of 8.4%. Incidence of surgical complications, specifically dural tears, was higher with increasing duration of leg pain, however, this did not reach statistical significance (p=0.039). Prolonged preoperative symptoms adversely influenced all PROs (EQ-5D,

ODI, VAS) one year after surgery (p=0.001). Furthermore, reoperation rates increased with longer duration of preoperative symptoms. A statistically significant trend (p=0.008) of increasing incidence of reoperation was found with increasing length of symptom duration.

**Conclusions:** Delayed surgical intervention results in inferior outcomes and increased reoperation rates. Patients who had surgery within the first 3 months of leg pain achieved significantly better outcome one year after surgery when compared to the other groups.

**Keywords:** Herniated disc • discectomy • duration of symptoms • PROs • patient reported outcomes • complications

## Introduction

Lumbar disc herniation (LDH) is associated with great morbidity and significant socioeconomic impact in many parts of the world [1-3]. Based on data from The Danish National Health Authority, 1-3% of the Danish population reported radicular pain due to LDH [4]. Approximately 2,000 Danes undergo operative treatment for this indication annually [5].

The majority of patients suffering from symptoms due to LDH can be treated effectively with non-surgical management. However, in some patients with severe pain and disability or whose recovery is unacceptably slow, surgical intervention can provide effective clinical relief [6-8]. Danish national clinical guidelines recommend that patients with LDH without neurologic deficits or intractable pain are managed with nonoperative treatment for up to 12 weeks before they are considered surgical candidates [9]. Currently there is little consensus in the medical community on the timing of surgery for patients suffering from radicular pain due to LDH.

Depending on the outcome measure used, 10-40% of patients report unsatisfactory results after lumbar disc surgery [10-12]. Many previous cohort studies have reported inferior results and adverse effects of prolonged preoperative symptoms [13-16]. Contrary to these, some randomized controlled trials (RCT) report no inferiority in outcome of patients with prolonged symptoms [10, 17, 18]. Systematic reviews on the subject find the same adverse effects as reported by most cohort studies [19]. Despite the relatively vast amount of literature available, no studies seem to have found the optimal time window to intervene and perform surgical treatment. Also, many of previously mentioned cohort studies suffer from relatively small patient populations, leading to uncertain results and conclusions. The largest previous study covering the subject is the SPORT study, which found inferior outcomes with prolonged symptom duration [16, 20]. The aim of the

current study is to investigate if prolonged symptom duration is correlated with less favorable outcome following surgery for LDH.

## Materials and methods

The current study is a retrospective cohort study using prospectively collected data from the Danish national surgical spine database (DaneSpine) [21]. DaneSpine collects patient reported outcomes (PROs) using pre- and postoperative questionnaires, completed before surgery and at 1, 2, 5 and 10 years postoperatively. The preoperative data are entirely patient reported, including age, sex, height, weight, duration of back and leg pain prior to surgery, back and leg pain on a 0-100 VAS scale [22], health-related quality of life as measured by the EuroQol-5D (EQ-5D) [23, 24], and spine-related disability as measured by the Oswestry Disability Index (ODI) [25, 26]. Duration of symptoms are collected as categorical values of <3-months, 3-12 months and >12-months. Surgical data are entered by the surgeon at the time of discharge from hospital and include diagnosis, procedure, antibiotic prophylaxis and occurrence of complications.

At follow-up, the same data registered at baseline is collected. At 1-year follow-up, patients are asked about their attitude towards the surgical outcome, with the options being: satisfied, neither satisfied nor dissatisfied and dissatisfied.

All patients who had surgery at the Center for Spine Surgery and Research, Middelfart Hospital, for a lumbar disc herniation with radicular pain from June 1, 2010 to May 1, 2017 were included. They had all followed the Danish national guidelines for treatment of patients with lumbar disc herniation [27], having received physiotherapy or other relevant exercise therapy before being referred from primary care to a spine specialist. None of the patients had cauda equina syndrome or severe neurologic deficits at the time of surgery. All had a magnetic resonance imaging (MRI) that demonstrated lumbar disc herniation, with the level and side corresponding with clinical symptoms. Baseline questionnaires were filled out no more than 1 week prior to surgery. Patients underwent discectomy by a senior consultant employed at the facility. Patients who had previous spine surgery

were excluded from further analysis. Subjects were divided into three groups based on their self-reported duration of leg pain prior to enrollment into the registry: <3-months, 3-12 months and >12-months.

## Patient and Public Involvement

The current study was done without patient involvement. As data originates from a database, it was not found feasible to involve patients in the study design nor the outcome measures, as these could not be changes. Patients were not invited to contribute to the writing or editing of this study for readability or accuracy.

## Statistics

All statistical analysis was done using STATA 15 (StataCorp., College Station, TX). Categorical data are presented by frequencies and related percentages; continuous data are displayed by means of descriptive statistics (mean, confidence interval, number of observations). Continuous variables were analyzed for significant difference between the three groups using analysis of variance (ANOVA), categorical variables using Fisher's exact test. Continuous variables found to change orderly across groups were analyzed using a Wilcoxon-type test for trend as developed by Cuzick (1985). Significance level was set at p-value <0.01. Adjustment for potential confounders was done using a forward stepwise regression analysis with an inclusion p-value of 0.10 and a confounding level of 15%.

## Results

During the nearly 7 years of inclusion, a total of 2,586 patients had surgery for a lumbar disc herniation causing radiculopathy. Of these, 442 (17.1%) had a history of previous spine surgery and were excluded from further analysis. Of the remaining 2,144 patients, 1-year follow-up data was available on 1,694 (79.0%). Most patients had surgery within one year of radicular leg pain onset, 613 (28.6%) with less than 3-months' history of leg pain, 1,095 (51.1%) with 3-12 months and 436 (20.3%) with more than 12 months.

Mean age for the entire cohort was 46.8 years and statistics indicating significant differences among groups, however only of 1-3 years. There were more males in the <3-month duration group (59.7% vs 52.2% vs 52.5%), with statistics indicating a significant difference in gender distribution. About one-third of the entire cohort (699, 32.7%) were active smokers at the time of surgery, and there was no statistically significant difference in the groups with longer history of leg pain (p=0.015). There was no difference in pain medication use or comorbidities among the three groups (Table 1). When asked about welfare payments, 22.9% (393) reported to receive welfare support, with no difference among the three groups.

*- Table 1 - Characteristics of the subgroup populations*

| | All (*n* = 2.144) | <3 months (*n* = 613) | 3-12 months (*n* = 1.095) | >12 months (*n* = 436) | *p*- value of difference |
|---|---|---|---|---|---|
| Age, mean (95 % CI) | 46.8 (46.2 ; 47.4) | 48.1 (47.1 ; 49.2) | 46.7 (45.8 ; 47.5) | 45.2 (43.8 ; 46.6) | 0.003 |
| Males, *n* (%) | 1.167 (54.4) | 366 (59.7) | 572 (52.2) | 229 (52.5) | 0.008 |
| Smokers, *n* (%) | 699 (32.7) | 173 (28.3) | 369 (33.8) | 157 (36.2) | 0.015 |
| Pain medication, *n* (%) | 1,939 (90.6) | 556 (90.7) | 1.001 (91.6) | 382 (88.0) | 0.101 |
| Comorbidities, *n* (%) | | | | | |
| *Heart disease* | 16 (0.8) | 2 (0.3) | 12 (1.1) | 2 (0.5) | 0.181 |
| *Neurological disease* | 31 (1.5) | 9 (1.5) | 12 (1.1) | 10 (2.3) | 0.193 |
| *Cancer* | 13 (0.6) | 2 (0.3) | 9 (0.8) | 2 (0.5) | 0.468 |
| *Other, affecting walking capabilities* | 74 (3.5) | 17 (2.8) | 35 (3.2) | 22 (5.1) | 0.122 |
| *Other, pain related* | 148 (6.9) | 40 (6.5) | 68 (6.2) | 40 (9.2) | 0.114 |
| Receiving welfare, *n* (%) | 491 (22.9) | 132 (21.6) | 249 (22.8) | 110 (25.3) | 0.368 |

Incidence of surgical complications, specifically dural tears, was higher with increasing duration of leg pain, however, this did not reach statistical significance (Table 2). Post-operative complications were diverse (Table 2) with hematoma being the most common but no significant differences found among groups.

As of December 1st, 2018, 179 (8.4%) patients had undergone reoperation within one year of primary surgery, 132 cases underwent repeat discectomy, 16 received additional decompression, 16 had a hematoma removed, three underwent drainage of infection, and 12 received other non-specified surgery. A statistically significant trend of increasing incidence of reoperation was found with increasing length of symptom duration. Approximately 17% of all patients who underwent re-operation did so during their primary admission.

*- Table 2 - Per- and postoperative complications*

| | All (n = 2.144) | <3 months (n = 613) | 3-12 months (n = 1.095) | >12 months (n = 436) | *p*- value of trend |
|---|---|---|---|---|---|
| Surgical complication, *n* (%) | | | | | |
| *Dural tear* | 60 (2.8) | 11 (1.8) | 32 (2.9) | 17 (3.9) | 0.039 |
| *Vascular damage* | 2 (0.1) | - | 1 (0.1) | 1 (0.2) | 0.235 |
| Postoperative complications, *n* (%) | | | | | |
| *Death* | - | - | - | - | - |
| *Trombosis* | - | - | - | - | - |
| *Emboli* | - | - | - | - | - |
| *Urinary tract infection* | 7 (0.3) | 1 (0.2) | 4 (0.4) | 2 (0.5) | 0.393 |
| *Urin retention* | 5 (0.2) | - | 3 (0.3) | 2 (0.5) | 0.121 |
| *Hematoma* | 16 (0.8) | 4 (0.7) | 6 (0.6) | 6 (1.5) | 0.233 |
| *Wound infection* | - | - | - | - | - |
| *Nerveroot lesion* | 6 (0.3) | 1 (0.2) | 4 (0.4) | 1 (0.2) | 0.775 |
| *Cauda Equina* | 5 (0.2) | 1 (0.2) | 1 (0.1) | 3 (0.7) | 0.121 |
| *Other* | 8 (0.4) | 3 (0.5) | 5 (0.5) | - | 0.229 |
| Reoperation, *n* (%) | | | | | |
| *Within 12 months* | 179 (8.4) | 38 (6.2) | 94 (8.6) | 47 (10.8) | 0.008 |
| *During primary admission (% of reoperated)* | 30 (16.9) | 6 (15.8) | 13 (14.0) | 11 (23.4) | 0.313 |

All groups had a significant improvement in EQ-5D, ODI, VAS leg pain and VAS back pain one year after surgery compared to baseline (Table 3). However, statistically significantly greater improvement in EQ-5D and ODI was seen in the <3-month pain duration group compared to the two other groups. In contrast, statistically significantly less improvement in VAS leg and VAS back was seen in the >12-month pain duration group compared to the two other groups (Figure 1).

All of the above outcome variables have been tested for potential confounding with regards to age, gender, BMI, smoking status, duration of backpain and whether the patient received social welfare or not (data not shown). Longer duration of backpain had a borderline significant negative effect on the outcome (p = 0.022) and patients receiving welfare at the time of surgery also showed better outcome at one year compared to those not receiving welfare (p <0.001). Smoking shows no significant effect on surgical outcome (p = 0.038). Age and BMI was not included in the model as neither significance level nor confounding level was above the set limits.

*- Table 3 - One-year PROM follow-up*

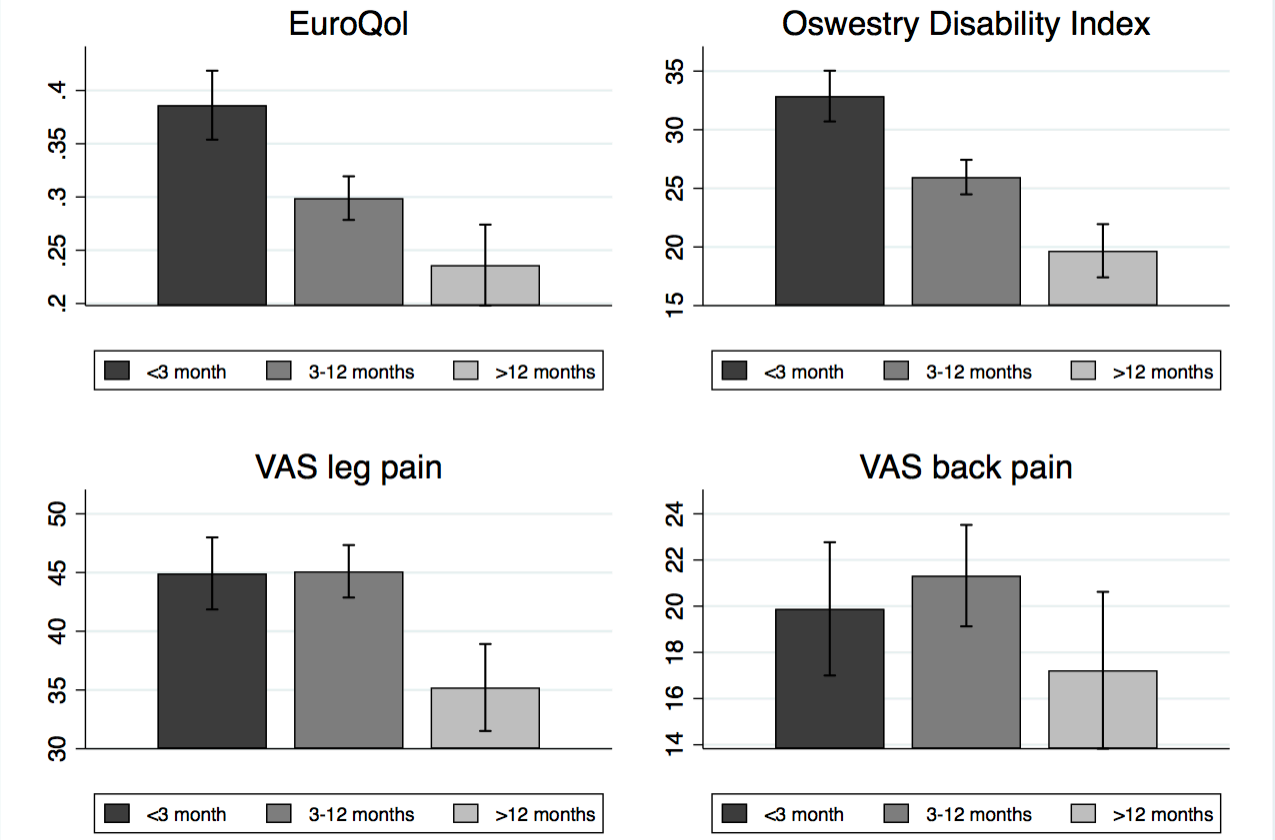
| | All (n = 2.144) | <3 months (n = 613) | 3-12 months (n = 1.095) | >12 months (n = 436) | *p*- value of trend |
|---|---|---|---|---|---|
| EQ-5D; mean (95% CI) | | | | | |
| *Pre-operative* | 0.45 [0.44;0.46] | 0.39 [0.37;0.42] | 0.47 [0.45;0.48] | 0.48 [0.45;0.50] | <0.001 |
| *Post-operative* | 0.77 [0.76;0.78] | 0.78 [0.76;0.80] | 0.77 [0.76;0.79] | 0.72 [0.70;0.75] | 0.001 |
| *Difference* | 0.31 [0.30;0.33] | 0.39 [0.35;0.42] | 0.30 [0.28;0.32] | 0.24 [0.20;0.27] | <0.001 |
| ODI; mean (95% CI) | | | | | |
| *Pre-operative* | 47.76 [46.97;48.55] | 52.14 [50.47;53.80] | 46.55 [45.54;47.56] | 44.69 [43.05;46.32] | <0.001 |
| *Post-operative* | 20.91 [20.05;21.77] | 19.36 [17.86;20.86] | 20.50 [19.31;21.69] | 24.25 [22.20;26.31] | 0.001 |
| *Difference* | 26.72 [25.62;27.83] | 32.87 [30.71;35.03] | 25.96 [24.49;27.43] | 19.68 [17.41;21.94] | <0.001 |
| VAS leg; mean (95% CI) | | | | | |
| *Pre-operative* | 67.76 [66.74;68.78] | 67.92 [65.85;69.99] | 67.94 [66.58;69.29] | 67.10 [64.87;69.33] | 0.138 |
| *Post-operative* | 24.39 [23.07;25.72] | 23.05 [20.72;25.37] | 22.51 [20.72;24.30] | 31.51 [28.17;34.85] | 0.001 |
| *Difference* | 43.16 [41.53;44.80] | 44.92 [41.86;47.99] | 45.10 [42.87;47.34] | 35.21 [31.51;38.91] | <0.001 |
| VAS back; mean (95% CI) | | | | | |
| *Pre-operative* | 48.10 [46.86;49.34] | 43.75 [41.39;46.12] | 48.82 [47.11;50.52] | 52.41 [49.69;55.12] | <0.001 |
| *Post-operative* | 26.89 [25.59;28.19] | 23.88 [21.67;26.10] | 25.99 [24.21;27.78] | 34.03 [30.73;37.32] | <0.001 |
| *Difference* | 20.12 [18.57;21.68] | 19.88 [17.00;22.77] | 21.32 [19.13;23.52] | 17.23 [13.83;20.62] | 0.436 |

## Discussion

This retrospective cohort study divides patients surgically treated for LDH into groups dependent on the duration of their preoperative symptoms. The present study found worse self-reported outcomes in patients with duration of preoperative leg pain of >3 months. Furthermore, a strong trend of increasing risk of reoperation was found with increasing duration of preoperative leg pain.

Previous literature as well as the present study shows that surgery for LDH is an effective treatment regardless of symptom duration [15]. Like previous studies, the current study population are patients in their forties with a slight majority of men [10, 17, 20]. The current study comprises more smokers than found in the general Danish population (i.e. 32.7% vs. 23%) [28]. Overall, this study's population seems comparable to that of earlier studies on symptom duration and outcome after surgery for LDH.

As shown in both Table 3 and Figure 1, longer preoperative duration of symptoms adversely affects clinical outcome in both EQ-5D, ODI and VAS leg pain. All groups reached clinically relevant improvements in the before mentioned parameters. The present study found a total postoperative complications risk of approximately 2%. The risk of reoperation increased with longer symptom duration and a trend analysis indicates that the timing of surgery is important, not only because of the poorer outcome, but also due to the risk of reoperation. The higher reoperation rates might also be affected by a lower surgeon and patient threshold in patients with longer preoperative leg pain if outcome is worse than expected. A subgroup analysis showed no difference in reoperation rates during primary admission.




*- Figure 1 - Change in patient-reported outcomes (PROs) at 1-year follow-up (mean; CI)*

Previous literature has found similar results, however with inconsistency regarding the timing of surgery. Nygaard et al. has previously found that surgical outcome is more favorable in patients with less than 6-months preoperative symptoms, when compared to both 6-12 months and >12-months of preoperative symptoms [13]. In a subsequent cohort study by the same lead author, patients with more than 8 months of preoperative leg pain were found to have less favorable outcome [14]. Both studies featured a relatively low number of patients, 93 and 132 respectively.

In 2015, Pitsika et al. [15] found statistically significant improvement in ODI regardless of preoperative duration, and advocated that surgery is indicated even after 1-2 years of symptoms. However, they also found a downward trend of improvement in ODI with increasing duration of symptoms. The study was a single surgeon sample, with follow-up on 97 patients (90.7 %). Thus, the sample size is relatively small, leading to small subgroups for further analysis. In a larger study, based

on the SPORT cohort, prolonged duration of symptoms was also found to have adverse effects on outcome, following both surgical and non-surgical treatment [16].

The major limitation of the present study is the retrospective analysis of data from a database and subsequent lack of full 1-year follow-up on all patients. A previous drop-out analysis on a similar population found that non-responders often were younger males, who were back at work and with better self-reported outcomes [29]. Thus, lack of complete follow-up is not likely to negatively affect results. Another major limitation is the fixed categorical intervals of duration of leg pain prior to surgery. Previous literature has suggested the "golden cut-off" timepoint to be somewhere around 6 months. The current intervals were chosen as a result of the data available in DaneSpine, however future studies should aim to measure duration of preoperative symptoms as continuous variables, thereby allowing for more detailed analysis to be performed.

Being a publicly funded institution, there are no economic barriers to undergo surgery at any time, and no bias in timing of surgery is instituted by insurance companies in the present study population. The study includes a large population of 2,144 consecutive patients, well dispersed in subgroups and no significant preoperative demographic differences. Patients are included consecutively, and all data collected prospectively at a single center for spine surgery.

All outcome variables were tested for potential confounders, and analysis showed borderline significant correlation with duration of backpain. This is, however, most likely due to collinearity with duration of leg pain as one is rarely present in complete absence of the other. If patients received social welfare at the time of surgery, they also had greater improvement in the beforementioned outcome variables at one-year follow-up. This might not be due to confounding, as an unsettled social welfare case would most likely lead to a surgical delay. However, as delayed surgery has negative correlation with outcome, it would be more plausible that social welfare status

is simply an isolated predictor. As published by Andersen et al., patients with prolonged sick leave have significantly lower return to work rate, compared to those with shorter duration sick leave prior to surgery [30]. This might also explain the poorer outcome in especially life quality at one-year follow-up, as patients are highly affected by their ability to take part in society i.e. work. Smoking, BMI and age could all have been relevant confounders, or even mediators, but no such relation was found.

The causal relation for prolonged duration of leg pain to cause inferior outcome is not immediately apparent. One might speculate in both psychological and somatic explanations. Previous literature suggests that prolonged sick leave, which would be more likely with prolonged symptom duration, leads to a lower chance of speedy return-to-work and therefore also a state of well-being with regards to serving society and a more purposeful living. There might also be a more biological relation both in respect of inflammatory processes and the tissues ability to repair/regenerate, or the brains more complex perception of pain and modulation of such. We know that surgery leaves a large immunological inflammatory response in the tissue, leading to great remodulation. If a disc herniation creates a similar response, and it persists for a prolonged duration of time, it might cause the surrounding tissue and structures to be less susceptible to recovery after the removal of the herniation. As a result, the pain may persist, thereby giving the patient an inferior surgical outcome. We have little certainty and knowledge about how the brain and spinal cord receives, modulates and translates pain, however science suggest that pain is very subjective and that the human brain has great power with regards to its modulation. One might speculate that with prolonged pain stimuli, i.e. that of a persistent disc herniation, the brains modulation of pain might change, and of such the conscious perception of pain would also change. This might in turn lead to a more permanent state, in which, the conscious part of the brain would perceive pain, despite the

fact, that the painful stimulus has been removed. Such hypothesis has previously been suggested and tested, but no clear evidence or consensus has been reached [31].

## Conclusion

In line with previous literature, the present study shows, that prolonged preoperative symptom duration adversely affects clinical outcomes in patients with LDH. Despite present data suggesting that the greatest treatment effect is achieved with the shortest duration of preoperative symptoms, the optimal timing of surgical treatment in LDH may be found in the interval of 3-12 months. Furthermore, the present study finds a greater risk of reoperation with longer duration of preoperative symptoms.

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## Appendix 2 – Manuscript II

# Utility of Preoperative Quantitative Sensory Testing in patients with Lumbar Disc Herniation

*Christian C. Støttrup[1,2] • Mikkel Ø. Andersen[1,2] • Leah Carreon[1,2] • Søren F. O'Neill[1,2]*

[1]Spine Center of Southern Denmark – Lillebaelt Hospital, Middelfart, Denmark

[2]Department of Regional Health Research – University of Southern Denmark, Odense Denmark

**Corresponding author:**

Christian C. Støttrup, MD

Spine Center of Southern Denmark – Lillebaelt Hospital, Middelfart, Denmark

Email: Christian.Stottrup@rsyd.dk

Phone: +45 2966 0602

**Purpose:**

Previous research has found different states of hypo- and hyperalgesia in patients with chronic pain conditions. As prolonged duration of preoperative symptoms can lead to altered pain perception and increased clinical pain, quantitative sensory testing (QST) and somatosensory profiling (SSP) could potentially be used to asses and perhaps quantify hyperalgesia in such conditions. This prospective cohort study investigates the predictive value of QST in patients with LDH scheduled for surgery.

**Methods:**

Patients scheduled for first episode LDH surgery were preoperatively tested using a standardized battery of QSTs. Patient-reported outcome (PRO) measures were collected both pre- and postoperative. Participants were divided into two separate somatosensory profiles (SSP) based on their preoperative QST results. The two groups were tested for differences in pre- and postoperative PROs. Associations between QSTs and PROs were evaluated.

**Results:**

A total of 63 participants were included, 8 of which were categorized with an altered SSP. No differences were found between the two SSPs in neither pre- nor postoperative PROs. Associations between QSTs and PROs were limited with conditioned pain modulation as the most promising parameter.

**Conclusion:**

No clinically relevant predictive value of QST was found in patients undergoing surgery for LDH. However, the outcomes of the included participants were more favorable than what is expected in a comparable cohort and therefore results should be interpreted with care. The clinical usefulness of QSTs in a spine surgery setup is most likely very limited.

**Keywords:** Quantitative sensory testing • lumbar disc herniation • discectomy • patient reported outcomes • predictive • outcome

## Introduction

Lumbar disc herniation (LDH), one of the more common spine disorders, can cause debilitating pain in otherwise healthy, self-supporting, and able-bodied individuals, leading to prolonged periods of sick leave, increased use of pain-medication and in some instances continuous bed rest.

In many cases the clinical course is self-limiting, with conservative care for attenuation of pain and spontaneous resolution within weeks. However, in other cases, surgery is needed to relieve the symptoms, but previous studies report unsatisfactory results in 10-40% of surgical cases, depending on the outcome measure used [1-3]. Although a few factors are known to have predictive value, it is generally difficult to preoperatively separate the patients who respond well to surgery, from those who do not [4].

Previous studies have found an association between chronic pain conditions and altered sensory perception of pain and other stimuli, leading to different states of hypo- or hyperalgesia [5, 6]. There is some evidence, that hyperalgesic changes in pain perception develop secondary to chronic pain and normalize following resolution of chronic pain, e.g. degenerative hip pain [7]. These findings suggest that prolonged symptom duration, could lead to altered pain perception and increased clinical pain. Quantitative sensory testing (QST) and somatosensory profiling could potentially be used to asses and perhaps quantify hyperalgesia in such conditions.

The purpose of the current study was to investigate whether preoperative QST can be used to identify patients who will have inferior clinical outcome following surgery for LDH.

## Material and methods

The current study was conducted as an experimental prospective cohort study in accordance with the STROBE guidelines [8]. Potential participant was given written and oral information on the purpose, nature and implications of study-participation. Information and inclusion of participants was conducted in accordance with the guidelines of The Health Research Ethics Committee System in Denmark. The study protocol was approved prior to commencing the study (S-20140052).

### Patient population and study course

All patients referred to and found eligible for LDH surgery at the Spine Center of Southern Denmark between September 2014 and December 2017 were consecutively asked to participate. Inclusion criteria were age between 18 and 70 years and MRI confirmed concordant single-level symptomatic lumbar disc herniation with indication for discectomy as assessed by an experienced spine surgeon. Furthermore, patients were not eligible if they had a history of previous spine surgery or a psychiatric history requiring medication during the last 3 months. Patients were also not eligible for inclusion if they presented with cauda equina syndrome or severe neurologic deficits at the time of surgery. Exclusion criteria included current malignant disease or ongoing treatment, a history of spinal fracture, hematologic disease, chronic, generalized connective tissue disorders or chronic, non-specific pain disorders (fibromyalgia, whiplash, etc.).

No more than two weeks prior to surgery, study participants underwent experimental assessment and quantification of pain sensitivity using a standardized QST battery, as described below. Demographic and clinical data on pain, physical function and health (PROMs) was collected using questionnaires from the Danish national surgical spine database (DaneSpine) [9]. QST

measurements were repeated 6 weeks and 6 months post-operative, whereas questionnaires were repeated 6 weeks (partially) and one- and two-years post-operative.

Participants underwent discectomy by a senior consultant at the facility. The clinical course of assessment, surgery, pre-surgical medication, post-surgical rehabilitation, etc. was not changed by participation in the study.

### Collection of QST data

The standardized QST battery consist of 3 different modalities, covering different measurements of pain perception and multiple types of pain stimuli. All measurements were performed in a quiet dedicated room with the participant comfortably seated or laying down.

Initially participants underwent a simple Pressure Pain Detection Threshold test (PPDT) using a handheld electronic pressure algometer (Somedic, Hörby, Sweden) at the thenar eminence of the hand and the most painful site of the lumbar area. Pressure was applied at a rate of 30 kPa/s using a 1 $cm^2$ probe. Participants were instructed to indicate when the applied pressure was perceived as just becoming painful, by pressing a button attached to the algometer. Two consecutive measurements were performed, and the mean values was defined as the Pressure Pain Detection Threshold.

Pain intensity at 140% of the individual PPDT was subsequently rated on a visual analog scale from 0-100 (VAS) and recorded as the Pain Response (PR) [10].

Next, participants underwent a Cold-Pressor Test (CPT) using a container of refrigerated water (0-2°C) in which they were asked to submerge their non-dominant hand to the wrist for 2 minutes. During the CPT, pain response, as it developed over time was monitored using an electronic continuous VAS (1 Hz). For individuals who failed to tolerate the entire 2 minutes, time of

withdrawal was recorded, and pain intensity was considered to be maximal for the remainder of the 2 minutes. Immediately following the CPT, participants were, once again, tested using the PPDT described above. This was performed to assess Conditioned Pain Modulation (CPM) in the central nervous system.

Finally, after a short break (approx. 3-5 min.), participants received an injection of 1 mL sterile hypertonic saline (58.5 mg/mL) at the infraspinatus muscle of the scapula. Once again, pain response was measured as it developed over time using a continuous VAS (0-100).

Using reference data, Magerl et al. for PPDT [11] and Neziri et al. for CPT [12], participants were dichotomized on the basis of their QST results, thereby dividing them into two distinct somatosensory profiles (SSP); normal and altered. An altered QST profile for PPDT was defined as a Z-score of minus two or less; for CPT it was defined as a withdrawal time below the $5^{th}$ percentile and/or area under the curve (AUC) above the $95^{th}$ percentile. All reference data comparisons were age and gender matched. Altered SSP was defined as two or more altered QST results.

### Collection of PROMs

All PROMs were retrieved from the Danish national surgical spine database (DaneSpine) [9]. Data was collected as previously described [13]. Variables collected were entirely patient reported, including age, sex, height, weight, duration of back and leg pain prior to surgery, back and leg pain intensity on a 0-100 VAS scale [14], health-related quality of life as measured by the EuroQol-5D (EQ-5D) [15, 16], and spine-related disability as measured by the Oswestry Disability Index (ODI) [17, 18].

## Statistics

All statistical analyses were done using STATA 16 (StataCorp., College Station, TX). A p-value of <0.05 was considered significant. All QST data were visually inspected for normal distribution using normal quantile plots and statistically tested using Shapiro-Wilk test for normality. If data were found to have a non-normal distribution, data were log10 transformed prior to further analysis.

Categorical data are summarized as frequencies and related percentages; continuous data are summarized as mean, standard deviation, and number of observations. Continuous variables were analyzed for significant between-group differences for the two SSP groups using student's t-test, categorical variables using Fisher's exact test.

A subsequent linear regression analysis was performed on all clinical outcome parameters (EQ5D, ODI, VAS and SF-36) to assess the correlation with QSTs. All regression analysis where adjusted for age and gender. Reported coefficients are unstandardized.

## Results

A total of 63 patients where included and one patient was subsequently excluded due to canceled surgery (spontaneous improvement of symptoms) leaving 62 participants for analysis. At the 1-year follow-up questionnaire, 13 did not respond despite multiple attempts of contact, resulting in a 1-year follow-up rate of 79%.

A total of 8 participants were found to have QST results outside of the reference values reported in previous studies, and therefore defined as having an altered SSP.

*° Table 1 - Characteristics of patient population, subgroup comparison based on somatosensory profile*

| | All (*n* = 62) | Normal SSP (*n* = 54) | Altered SSP (*n* = 8) | *p* -value of difference |
|---|---|---|---|---|
| Age, mean (SD) | 46.8 (11.4) | 46.8 (11.8) | 46.8 (8.48) | 0.992 |
| Males, *n* (%) | 33 (53.2) | 31 (57.4) | 2 (25.0) | 0.131 |
| Smoking, *n* (%) | 14 (22.6) | 12 (22.2) | 2 (25.0) | 1.000 |
| BMI, mean (SD) | 25.6 (3.35) | 25.7 (3.36) | 24.9 (3.35) | 0.512 |
| Duration of legpain >1 year, *n* (%) | 10 (15.9) | 9 (16.4) | 1 (12.5) | 1.000 |
| EQ5D baseline, mean (SD) | 0.53 (0.23) | 0.54 (0.22) | 0.50 (0.30) | 0.657 |
| ODI baseline, mean (SD) | 41 (15.3) | 40.5 (14.8) | 44 (19.1) | 0.557 |
| VAS back-pain baseline, mean (SD) | 42.5 (27.9) | 43.7 (27.5) | 34.5 (31.7) | 0.387 |
| VAS leg-pain baseline, mean (SD) | 64.3 (19.7) | 64.3 (19.4) | 63.9 (23.0) | 0.952 |
| SF-36 PCS baseline, mean (SD) | 32.1 (7.13) | 31.8 (7.38) | 34.1 (5.01) | 0.386 |
| SF-36 MCS baseline, mean (SD) | 46.3 (9.94) | 46.1 (10.0) | 47.4 (9.90) | 0.746 |

## Demographics

Mean age was 46 years of age, with no significant difference between the two groups. The altered SSP group had a higher proportion of females and had a longer duration of leg pain, but this difference was not statistically significant (Table 1). Patient reported outcome measures at baseline and at one-year follow-up were similar between the two groups (Table 2).

## Regression analysis

Two of the six linear regression models found significant associations (Table 3) between QST parameters and PROs. VAS back had a statistically significant association with the conditioned pain modulation parameter of the thenar. SF-36 Physical Component Score (PCS) showed significant associations with the AUC of the saline injection VAS measurement. None of the other variables were significantly associated. The individual models $r^2$ ranged from 0.140 to 0.328, and 4 out of 6 models was found to have negative adjusted $r^2$ values (data not shown).

*° Table 2 - Clinical outcome at 1-year, subgroup comparison based on somatosensory profile*

| | All ($n$ = 62) | Normal SSP ($n$ = 54) | Altered SSP ($n$ = 8) | $p$-value of difference |
|---|---|---|---|---|
| EQ5D, mean (SD) | 0.86 (0.14) | 0.86 (0.14) | 0.85 (0.13) | 0.936 |
| ODI, mean (SD) | 11.6 (9.52) | 11.7 (10.1) | 10.4 (2.97) | 0.770 |
| VAS back-pain, mean (SD) | 14.0 (20.9) | 12.6 (18.1) | 26.2 (39.2) | 0.172 |
| VAS leg-pain, mean (SD) | 8.29 (12.2) | 8.81 (12.7) | 3.80 (4.76) | 0.390 |
| SF-36 PCS, mean (SD) | 48.1 (8.68) | 48.2 (9.08) | 47.0 (4.06) | 0.766 |
| SF-36 MCS, mean (SD) | 55.0 (8.58) | 54.6 (8.86) | 58.2 (5.08) | 0.382 |

## Discussion

This prospective cohort study investigates the predictive value of QST in patients with LDH scheduled for surgery. Participants were divided into two groups based on their SSP, derived from their preoperative QST results. No statistically significant difference was found between the two groups on their preoperative demographic, clinical data or the PRO measures one-year postoperative. A subsequent multiple regression analysis indicated an association between conditioned pain modulation and VAS back-pain and an association between AUC VAS of a standardized saline injection and SF-36 PCS.

In previous literature QSTs and different types of somatosensory profiling has been proven effective in the identification of generalized hyperalgesia and hypersensitivity to experimental pain stimulus in a multitude of chronic pain conditions [6, 19-24]. Furthermore, previous literature has found that individuals with chronic pain conditions often have both localized and generalized hyperalgesia [21]. As such, one would expect hyperalgesia to manifest in conjunction with development of chronic pain. However, in the current study we find no indication of prolonged symptom duration in the altered SSP group. The increased duration of leg pain would otherwise be indicative of development of chronicity. This may however be due to the patient population, as LDH is not known to cause chronic pain.

Several studies have found chronic low back pain (LBP) patients to have significant deep-tissue hyperalgesia when compared to healthy controls [5, 6]. A case-control study of patients with radiologically verified LDH and corresponding radicular pain in the lower limb reported similar findings [6]. These cases therefore resemble the ones in the current study, however they differ in that they did not present with indication for surgery. One would, however, expect that the

participants in the current study would demonstrate a level of hyperalgesia if compared to matched healthy controls.

The same authors also published a study concluding that low pressure pain thresholds are not an isolated risk factor of future LBP, however, they found that patients with long-lasting LBP are more likely to suffer from hyperalgesia compared to those with no or short-lasting LBP [21]. This is in agreement with the present study, as we find no predictive value of QSTs and an altered SSP.

The present study found very few associations between QST parameters and the most commonly used PROs in spine surgery. This is in agreement with previous literature comparing these measures. Tschugg et al. has previously compared QST and clinical parameters at baseline and 12-months post-operative in LDH patients who underwent discectomy [24]. Their conclusion was that there is low or no correlation between QST parameters and clinical scores. The same conclusion was reached in a systematic review by Sangesland et al. looking at the association between experimental pain stimuli and their predictive value on post-operative pain [23]. The surgical procedures of the included studies were diverse, but the conclusion was that QSTs does not consistently predict outcome with relation to pain intensity.

*° Table 3 - Linear regression with clinical outcome measures as dependent variables and QST measures as independent variables*

| | 1-year EQ5D | 1-year ODI | 1-year VAS back | 1-year VAS leg | SF-36 Physical | SF-36 Mental |
|---|---|---|---|---|---|---|
| | Coef. (*p* -value) | Coef. (*p* -value) | Coef. (*p* -value) | Coef. (*p* -value) | Coef. (*p* -value) | Coef. (*p* -value) |
| Pressure Pain Detection of thenar* | -0.0453 (0.808) | 1.954 (0.884) | -15.38 (0.553) | 2.945 (0.854) | 1.635 (0.878) | -4.021 (0.740) |
| Pressure Pain Detection of lumbar* | 0.0986 (0.459) | -7.494 (0.339) | -2.556 (0.872) | -11.87 (0.233) | 7.618 (0.240) | -0.250 (0.973) |
| Pressure Pain Response VAS | 0.00115 (0.434) | -0.0103 (0.924) | 0.0922 (0.655) | 0.0608 (0.638) | 0.0670 (0.431) | -0.00580 (0.952) |
| CPT withdrawal time | 0.000435 (0.591) | -0.0260 (0.638) | -0.0303 (0.789) | 0.0587 (0.406) | 0.0111 (0.809) | -0.0521 (0.322) |
| CPT AUC | 0.00000571 (0.709) | 0.000161 (0.872) | 0.000942 (0.647) | 0.0000138 (0.991) | 0.000163 (0.845) | -0.000491 (0.604) |
| Saline AUC | -0.00000493 (0.115) | 0.000245 (0.254) | 0.000685 (0.120) | -0.000173 (0.516) | -0.000389 (0.032)* | -0.000121 (0.544) |
| Change in Pressure Pain Detection of thenar | 0.0000500 (0.850) | -0.00673 (0.661) | 0.0778 (0.018)* | -0.00483 (0.807) | -0.00261 (0.839) | -0.0195 (0.188) |
| Change in Pressure Pain Detection of lumbar | -0.000366 (0.235) | 0.00830 (0.685) | -0.0363 (0.357) | 0.00959 (0.701) | -0.000920 (0.954) | -0.00544 (0.763) |
| Change in Pressure Pain Response | 0.00220 (0.311) | -0.223 (0.153) | 0.0755 (0.805) | -0.0917 (0.640) | 0.197 (0.125) | 0.0268 (0.852) |
| Constant | 0.802 (0.151) | 16.78 (0.665) | 30.62 (0.689) | 22.02 (0.640) | 31.88 (0.315) | 81.42* (0.029) |
| R-squared | 0.253 | 0.219 | 0.268 | 0.111 | 0.328 | 0.147 |
| Number of observations | 44 | 43 | 47 | 46 | 46 | 46 |

The present study is in some ways comparable to the two studies by Lindbäck et al. which examined the predictive value and usefulness of experimental pain stimuli in patients with LDH and spinal stenosis [20, 25]. The patient cohort was a combination of spinal stenosis and LDH, but all were scheduled for spine surgery. Patients were tested with a battery of QSTs prior to surgery, and a 3-months post-operative questionnaire was used to evaluate PRO measures. The authors report altered SSPs in 22% of the cohort and significantly increased preoperative VAS for both leg and back pain. No statistically significant differences in outcome measures between the two SSPs were reported. In a subsequent regression analysis on LDH patients only, the authors reported an association between increased sensitivity to pressure pain and lower preoperative ODI. The same association was found with regards to post-operative ODI and VAS leg pain.

These results are somewhat contradictory to the findings of the present study, as we find no differences between the two SSP groups in neither the preoperative parameters, nor the post-operative outcome measures. Similarly, the results of regression analyses are not aligned between the present study and those of Lindbäck et al.

The reason for these differences may lie with the cohort itself. Comparing the two cohorts show that the number of patients with prolonged (>2 years) duration of preoperative leg pain was significantly higher in the study population of Lindbäck et al. (data for current study not shown). This, in conjunction with the fact that mean VAS back and leg pain where higher in the Swedish cohort may constitute the demographic differences between the two cohorts.

In the regression analysis, Lindbäck et al. found an association between PPT and both pre- and post-operative outcome measures. These findings cannot be replicated in the present study. Once more, considering the cohort, we find that the participants in the current study seem to obtain clinically relevant superior outcome when it comes to post-operative pain, function and health. These

dissimilarities in postoperative outcome might be a result of the differences in preoperative duration of pain and may very well alter the conclusions in unknown ways.

### Strengths and weaknesses

In the current study, QSTs and derived SSP are used as a surrogate measure of pain perception and hypersensitivity. These assumptions introduce some caveats and limitations which should be considered carefully. As all participants in the current cohort underwent QST on the day they were found eligible for surgery. This means many, if not all, were using pain medication of some sort. This in turn may affect the results of the QSTs.

Furthermore, participants had additional follow-up, due to the QSTs, compared to standard care, which could potentially bias them in a positive direction with regards to outcome measures. Many previous studies have shorter follow-up which may also change the results of PRO measures, as a change in hypersensitivity may very well normalize during the time of a one-year follow-up. Lastly, the current study has a relatively small sample size, albeit the largest to our knowledge on a comparable cohort.

## Conclusion

This prospective cohort study investigating the use of QSTs in patients undergoing surgery for LDH found no clinically relevant predictive value of such tests. however, these results should be interpreted with care, as the PRO measures of the cohort in general was more favorable than what is expected in a comparable general cohort. The predictive value of QSTs can therefore not be rejected outright, but the present results in combination with existing literature, suggests the clinical usefulness of such test in a spine surgery setup is most likely very limited.

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## Appendix 3 – Manuscript III

# "Visualization" of pain using 18-FDG PET/CT of the brain

*Christian Christensen Støttrup*[1,2] • *Caius Constantinescu*[3,4] • *Reza Piri*[3,4] • *Mohsen Khosravi*[5] • *Mikkel Østerheden Andersen*[1,2] • *Abass Alavi*[5] • *Poul Flemming Høilund-Carlsen*[3,4]

[1]Center for Spine Surgery and Research, Lillebaelt Hospital, Middelfart, DENMARK

[2]Department of Regional Health Research, University of Southern Denmark, Odense, DENMARK

[3]Department of Nuclear Medicine, Odense University Hospital, Odense, DENMARK

[4]Department of Clinical Research, University of Southern Denmark, Odense, DENMARK

[5]Department of Radiology, University of Pennsylvania, Philadelphia, USA

**Corresponding author:**

Christian C. Støttrup, MD

Spine Center of Southern Denmark – Lillebaelt Hospital, Middelfart, Denmark

Email: Christian.Stottrup@rsyd.dk

Phone: +45 2966 0602

**Purpose** We hypothesised that unilateral leg pain following surgical treatment of lumbar disc herniation (LDH) is associated with an increase in the glucose metabolism of the contralateral thalamus, since previous studies have found such an association with regard to cerebral flow.

**Methods** Patients scheduled for surgery due to LDH underwent $^{18}$F-fluoro-deoxy-D-glucose positron emission tomography / computed tomography (FDG-PET/CT) less than two weeks prior to surgery. Their thalamic FDG uptake was measured using semi-automated processing software (ROVER, ABX, Radeberg, Germany) and expressed as the maximal, mean and partial volume corrected mean standardized uptake values (SUVmax, SUVmean, and cSUVmean). These measures were compared with patient-related outcome measures collected pre- and 1-year postoperatively: back and leg pain on a 0-100 VAS scale, health related quality of life as measured by the EuroQol-5D (EQ-5D), and spine-related disability as determined by the Oswestry Disability Index (ODI).

**Results** Twenty-six patients (10 females) aged 49.7 ± 7.4 (mean ± SD) years were included in the analyses. Twenty-two had a preoperative symptom duration of less than one year with mean 39.5 and 65.3 VAS back and leg, respectively. SUVmax data did not suggest any association between painful body side and increased contralateral thalamic uptake of FDG, whereas there was an insignificant trend when estimated from SUVmean data and a significant association with cSUVmean values. Correlation analyses including clinical parameters and cSUVmean indicated some association with 1-year change in EQ-5D.

**Conclusion** Our preliminary data sustain the hypothesis that unilateral pain in patients with LDH is associated with increased glucose metabolism in the contralateral thalamus, suggesting a central role of thalamus in chronic pain perception.

**Keywords** Pain • Pain perception • PET • 18F-FDG • Lumbar disc herniation • Thalamus • Quantification

## Introduction

In modern society, pain and its treatment may lead to great morbidity among patients. Many pain conditions require medication that often leads to use and even abuse of opioids. The latter "spillover effect" further burdens the healthcare system with chronically afflicted patients and leads to severe cost expenditure for individuals and society [1-3]. We do not really know what pain is, but we are aware that pain conditions have a negative impact on most individuals' physical and psychosocial health. Consequently, research in pain and its management aim for a better understanding of pain and pain perception. In addition, there is a need for a quantifiable measure to compare pain between individuals and monitor effects of pain therapy.

With modern imaging techniques we are able to assess and even quantify nutrient uptake in cells, thereby obtaining a measure of cell metabolism. In the nervous system, and particularly the brain, changes in cell metabolism may very well be a surrogate measure of regional cerebral cell activity. In a former study by Newberg et al. single-photon emission computed tomography (SPECT) was used to analyze cerebral blood flow in patients with chronic pain conditions [4]. Their findings indicated that following acupuncture therapy, cerebral blood flow changed in the frontal lobes and the thalami. These changes were thought to correlate with pain perception of the patients and therefore were suggested as a surrogate measure of quantifiable pain perception.

Patients with lumbar disc herniation (LDH) have primarily unilateral pain radiating to one of their legs. This unilateral pattern creates the foundation for comparing how pain stimuli affect brain cell metabolism across the two hemispheres. We hypothesized that unilateral pain of LDH patients will increase metabolism in the thalamus of the contralateral hemisphere and be detectible using positron emission tomography/computed tomography with 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose (FDG-

PET/CT). Furthermore, that such visualization would be quantifiable and correlate with patient-reported pain perception and clinical outcome measures.

## Materials and methods

### Patient population and study course

Between September 2014 and September 2015 all patients aged 40-65 years, who after referral were found eligible for surgery at a major Danish degenerative spine center due to LDH were asked to participate in the study. Exclusion criteria were pregnancy, malignant disease, prior radiation treatment, spine surgery or spinal fractures, psychiatric disorders and chronic pain conditions not attributable to LDH, i.e., generalized connective tissue disorders, chronic regional pain syndrome, etc. All eligible patients who gave consent to participation underwent an FDG-PET/CT scan no more than two weeks prior to surgery. Demographics and data on pain, physical function and health were collected using questionnaires from the Danish national surgical spine database (DaneSpine) [5]. All participants received the standard care of the spine center, and surgery was performed by a senior consultant using ordinary discectomy or minimally invasive surgical approach.

### PET/CT imaging

Patients were asked to refrain from pain medication 36 hours (5 x the half-life of relevant drugs) prior to their PET/CT scan and were kept fasting for at least 6 hours before their scan. They were placed supine on the tomography bed in a quiet room with dim lighting and their head was immobilized with a dedicated headrest. Following 10 minutes of rest, FDG (4 MBq/kg body weight) was administered intravenously. Images were obtained using an acquisition protocol with 47 slices (3.3 mm) in each frame on a General Electric Discovery PET/CT 690 or 710 scanner. A complete PET/CT scan from the top of the head to the sacrum was performed and the data from 60-90 minutes were summed and used for analyses. All scans were performed at the Department of

Nuclear Medicine, Odense University Hospital, in accordance with local standard operating procedures.

PET images were segmented and analyzed using ROVER software (v2.1 ABX, Radeberg, Germany). Proper head alignment was examined prior to defining region of interest (ROI). Head tilt was corrected manually on the CT using a global pixel shift, thereby not altering pixel size or values. After fusing the PET/CT using DICOM information, a rigid correction for head movement on the PET image was done in order to ensure proper PET/CT overlap. Subsequently, an ovoid ROI was defined by the observer on a scan-to-scan basis to best fit the thalamus structure in one hemisphere. This mask was then duplicated in exact size and shape and applied to circumscribe the contralateral thalamus.

A lower fixed threshold of 41% of the peak standardized uptake value (SUV) was applied to exclude cerebrospinal fluid activity and the spillover from other surrounding structures. For each of the segmented regions, ROVER calculated the volume of the ROI together with the following range of SUV metrics: maximum, mean, mean partial volume corrected, which were designated SUVmax, SUVmean, cSUVmean, respectively. Prior to further analysis of PET/CT data, all patients were tested for hemispheric diaschisis in order to eliminate any generalized cerebral metabolic lateralization. In brief, diaschisis is the finding of a remote functional disturbance in a region connectively related to a focal brain damage area. The presence of diaschisis is searched for by calculating the total hemispheric glucose metabolism ratio (THGr) as described by Segtnan et al. [6].

### Collection of patient-reported outcome measures

All patient-reported outcome measures were retrieved from the Danish national surgical spine database (DaneSpine) at baseline and one-year follow-up [5]. Data was collected as previously

described [7]. Variables collected were entirely patient-reported, including age, sex, height, weight, duration of back and leg pain prior to surgery, back and leg pain on a 0-100 VAS scale [8], health-related quality of life as measured by the EuroQol-5D (EQ-5D) [9, 10], and spine-related disability as measured by the Oswestry Disability Index (ODI) [11, 12].

## Ethics

The current study was performed as an experimental prospective cohort study in accordance with the STROBE guidelines [13]. Patients were given written and oral information on the purpose, nature and implications of study participation. Information and inclusion of participants was conducted in accordance with the guidelines of The Health Research Ethics Committee System in Denmark, by which the study protocol was approved prior to commencing the study (S-20140052).

## Statistics

All statistical analyses were performed with STATA 16 (StataCorp., College Station, TX). As the number of observations were low, a p-value of $<0.05$ was considered significant. Categorical data are presented by frequencies and related percentages; continuous data are displayed by means of descriptive statistics (mean/median, range, number of observations). Categorical variables and contingency tables were analyzed for significant difference using Fisher's exact test. Continuous variables were analyzed for correlations with PET/CT parameters using Spearman's rank correlation coefficient test. Correlation coefficients of $<0.40$ were considered weak.

## Results

A total of 32 patients were originally included in the study. Of these 5, did not undergo a baseline PET/CT scan and one patient experienced spontaneous symptom relief and, thus, did not undergo surgery leaving a total of 26 patients (16 males) with baseline PET/CT to be included in the analysis. They had a mean age of 49.7 years and a mean BMI of 26.3 (Table 1). Twenty-two underwent surgery within one year from onset of radicular leg pain, while 4 (15.4%) had a symptom duration of more than one year at the time of surgery. At baseline, patients reported an EQ-5D of 0.53 and an ODI of 42.9. VAS back and leg was 39.5 and 65.3, respectively (Table 1).

When testing for cerebral diaschisis we found the following THGr values for the entire material without outliers: mean 0.96, median 0.98, range 0.89-1.00, i.e., values indicating normal conditions according to previous literature [6, 14]. SUVs in left and right thalamus are displayed in Table 2.

Of the 26 patients with baseline PET/CT scans, 25 reported unilateral radiating leg pain in conjunction with some degree of back pain. The side to which the pain was radiating, was registered using the baseline questionnaire and was used to test the hypothesis of lateralization of thalamic metabolism in conjunction with unilateral pain. One patient reported bilateral radicular leg pain and was therefore not included in these analyses. For each of the abovementioned SUV metrics, the hemisphere with the highest thalamic SUV measure (max, mean and partial volume corrected mean) was noted and compared to the side of radicular leg pain. Numbers were entered into a contingency table and results were evaluated. For SUVmax no clear pattern was found, whereas SUVmean and cSUVmean showed lateralization towards the thalamus of the hemisphere contralateral to the registered pain side (Table 3). Using the Fisher's exact test, statistics showed significance for cSUVmean (*p*-value 0.027).

† *Table 1 - Characteristics of patient population, n = 26*

| | |
|---|---|
| Age, mean (SD) | 49.7 (7.35) |
| Males, *n* (%) | 16 (61.5) |
| BMI, mean (SD) | 26.3 (3.72) |
| Duration of legpain >1 year, *n* (%) | 4 (15.4) |
| EQ-5D baseline, mean (SD) | 0.53 (0.21) |
| ODI baseline, mean (SD) | 42.9 (12.7) |
| VAS back-pain baseline, mean (SD) | 39.5 (26.2) |
| VAS leg-pain baseline, mean (SD) | 65.3 (20.6) |

To investigate if the PET/CT scan metrics correlated with the clinical parameters reported by the patients, a mean thalamic glucose metabolism ratio (MTGr) was computed. The cSUVmean of the thalamus contralateral to the pain side was indexed to the ipsilateral thalamic metabolism, resulting in MTGr values, which – when above one – indicated the hypothesized relation between metabolism lateralization and pain side.

† *Table 2 - FDG-PET/CT measurements of the right and left thalami of included patients*

| | Right (*n* =26) | Left (*n* =26) |
|---|---|---|
| Max SUV, median (min;max) | 12.20 (9.1;19.7) | 12.05 (9.2;20.2) |
| Mean SUV, median (min;max) | 8.20 (6.1;13.6) | 8.20 (6.2;13.6) |
| Mean SUV PVC, median (min;max) | 8.85 (6.5;14.7) | 9.00 (6.6;14.2) |

The computed MTGr was evaluated for correlations with patients' reported pain perception and subsequent clinical outcome measures. Correlation coefficients for baseline pain perception and self-reported quality of life were generally low ($\rho$<0.40) and none reached statistical significance.

As only 18 of the 26 patients followed the hypothesized contingency table, a separate correlation analysis was run on these patients in order to see if that produced better correlation coefficients. The correlation between MTGr and EQ-5D showed a coefficient of -0.47 (*p*-value 0.048), but once more, the remaining coefficients indicated weak correlations.

To test if lateralization of thalamic metabolism was associated with clinical outcome of surgical treatment, a Spearman's rank correlation test was set up between MTGr and the 1-year change scores of patients reported outcome measures. A correlation coefficient of -0.50 (*p*-value 0.068) was found between MTGr and change in VAS back pain. The remaining coefficients all indicated weak correlations ($\rho$<0.40). If stratifying the patients to only include the ones mentioned earlier (fitting the hypothesis), the correlation with EQ-5D change score was 0.54, but statistically non-significant (*p*-value 0.167). The before mentioned moderate correlation with the change in VAS back pain became very weak ($\rho$<0.20), however, the coefficient between MTGr and change in VAS leg pain rose to -0.51 (*p*-value 0.194).

*† Table 3 - Comparison of painful body side and increased PET/CT activity in the thalamus*

| | Painful body side | | |
|---|---|---|---|
| Increased PET/CT activity | Right | Left | *p* -value |
| **Max SUV**, *n=25* | | | |
| Right, *n* (%) | 5 (20%) | 4 (16%) | |
| Left, *n* (%) | 6 (24%) | 10 (40%) | 0.325 |
| **Mean SUV**, *n* =25 | | | |
| Right, *n* (%) | 4 (16%) | 9 (36%) | |
| Left, *n* (%) | 7 (28%) | 5 (20%) | 0.163 |
| **Mean SUV PVC**, *n* =25 | | | |
| Right, *n* (%) | 2 (8%) | 9 (36%) | |
| Left, *n* (%) | 9 (36%) | 5 (20%) | 0.027* |

## Discussion

We found a statistically insignificant/significant pattern of an increase in thalamic glucose metabolism contralateral to the painful body region. Furthermore, there was a moderate correlation between quality of life and the ratio of thalamic glucose metabolism in patients with increased metabolism contralateral to their painful body side. A similar slight, but statistically insignificant, correlation, was found with regard to change in VAS back and leg pain.

Only a very limited amount of literature exists on changes in cerebral glucose metabolism as a result of pain perception and, therefore, direct comparisons to previous published results are not an option. As there is no standardized protocol for using PET/CT to quantify changes in brain metabolism as a result of painful stimuli, we chose to use the European Association of Nuclear Medicine procedure guidelines for tumour imaging in the acquisition of SUV metrics [15]. This was done to apply known methods for quantifying metabolism and to facilitate an easier reproduction of the techniques applied.

In order to analyze and quantify lateralization in the thalamus of each hemisphere we tested for and found no signs of general cerebral diaschisis as previously described by Segtnan et al. [6]. Both the median and range of the SUV metrics for the cerebral hemispheres were compared with previously reported findings of a median cerebral hemisphere ratio of 0.95, ranging between 0.65-1.00 in healthy individuals. The present findings with a median of 0.98, ranging 0.89-1.00 are clearly within what can be considered normal and, thus, were an indication of absence of cerebral hemispheric diaschisis.

We hypothesized that unilateral pain would lead to an increased glucose metabolism of the contralateral thalamus as a result of the afferent synapse in the somatosensory pathway. The results in Table 3 show no tendency of such a pattern with regards to SUVmax measurements. There are

multiple potential explanations for this, one being that the afferent synapses are relatively scattered in the thalamus and, therefore, do not lead to a single hotspot. In contrast, both SUVmean and cSUVmean indicated a contralateral relationship between pain and increase in thalamic activity. The increased significance level of the partial volume corrected measure may be due to the small volume of the thalamus and consequent higher relative influence of the correction for partial volume effect [16]. The reason for using the ratio between the two hemispheres, as opposed to the nominal values, was to make the individual patients serve as their own controls to adjust for any inter-scan differences which might otherwise skew the results.

As far as we know, the findings here are the first quantitative cerebral glucose metabolism results reported in surgical candidates with LDH. A previous study by Newberg et al. found significant asymmetry in thalamic blood flow using SPECT in patients with chronic pain syndrome [4]. Their findings indicated a significantly higher degree of lateralization in patients with pain compared to healthy controls. Despite being measures of cerebral blood flow and not metabolism, one would expect those two parameters to present some collinearity. Similar results were reported by Guillot et al., who found significantly increased thalamic activity in cats with osteoarthritis-associated pain [17]. Contrary to these findings, Iadarola et al. used oxygen-15 water bolus PET to image cerebral activity in 4 patients with post-traumatic neuropathic pain [18]. They reported a decreased blood flow in the thalamus contralateral to the symptomatic side.

Correlations between quantitative measurements of glucose metabolism in the thalamus and clinical measures (VAS, disability and quality of life) were found to be moderate at best, and only when excluding patients not conforming with the abovementioned hypothesis of increased activity contralateral to the symptomatic side, did we find statistically significant correlations. This may lead to speculations on whether a correlation actually exists, as the coefficients were only moderate, and

scatterplots of the observations did not indicate a convincing pattern (data not shown). The correlations with EQ-5D were the most consistent and indicated a worse quality of life at baseline when a higher ratio between the two thalami was measured. Likewise, a higher change in EQ-5D was observed at 1-year when the ratio increases. This harmonizes well with the hypothesis that increased lateralization is indicative of a chronic pain condition and subsequently decreased physical and psychological well-being. When correlating the glucose metabolism ratio with pain perception measured by VAS leg- and back pain, the results were much more diverse, and, therefore, less likely to be consistent in a larger cohort.

We acknowledge that our relatively small cohort is a limitation, as any observation will need to produce a relatively uniform and large signal to come out significant. This also means that any outliers will skew the results towards a type II error. A further limitation of unknown proportion is the patients' use of pain medication, which was not recorded. Despite being asked not to take pain medication in five times the half-life of each drug before the PET/CT scan, the actual compliance with this instruction was unknown. Furthermore, the described method of quantifying glucose metabolism was only partly standardized and, therefore, probably somewhat observer dependent.

## Conclusion

The current study sustains the hypothesis that unilateral pain of LDH patients is associated with an increase in the metabolism of the thalamus of the contralateral hemisphere in line with the suggestion that thalamus may operate as some sort of a "relay station" in pain perception. Whether there is a nominal relation between metabolism ratio and subjective pain perception is unclear, however, our data seem to suggest that quality of life is negatively affected by a higher degree of thalamic imbalance. Further research is needed, preferably using high resolution scanners and MRI

segmentation, to confirm if our preliminary findings hold water and can serve as a basis for optimized post-surgery pain management in LDH.

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