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Pathoanatomical contributors to lumbar spinal stenosis

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Abstract

Objective: To investigate the association and relative contribution of facet joint hypertrophy and disc degeneration, particularly posterior disc bulging, with dural sac cross-sectional area and the prevalence and severity of lumbar central canal stenosis in a general adult male population.

Methods: 197 adult males from the Twin Spine Study were included in the study. Using axial MRI scans of the lumbar spine, central canal stenosis, facet joint hypertrophy, and posterior disc bulging were assessed at the L2/3 through L5/S1 spinal levels. Previously established measurement techniques and grading criteria were used to assess the structures of interest.

Results: Facet joint hypertrophy and posterior disc bulging were inconsistently associated with central canal stenosis when analyzed by spinal level, except for a consistent association of posterior disc bulging with qualitatively assessed LSS across all levels. Posterior disc bulging was also associated with both canal capacity (R^2=0.06, p=0.002) and qualitatively assessed central canal stenosis (OR=2.3, p=0.001) when considering the combined levels of L3/4 and L4/5.

Conclusion and significance: Posterior disc bulging appears to play a more significant role in central canal stenosis than facet joint hypertrophy. However, both structures explained little of the variance in canal capacity or the odds of having stenosis, suggesting that other factors may be of greater importance. Further research using larger samples that can support more refined measures of facet joint hypertrophy, disc degeneration and stenosis is needed to clarify their associations and confirm and expand our study findings.

Keywords

Lumbar spinal stenosis, dural sac cross-sectional area, relative stenosis, absolute stenosis, facet joint hypertrophy, intervertebral disc degeneration, disc bulging.

Summary for Lay Audience

Lumbar (low back) spinal stenosis is a narrowing of the spinal canal resulting in compression of the neurovascular tissues contained within. Spinal stenosis is a common source of pain and disability among older adults and is the most common reason for spinal surgery in individuals older than 65 years of age. The clinical symptoms of lumbar spinal stenosis include low back pain with or without radiating pain to the lower limbs, lower limb numbness, and pain during walking or standing. Narrowing of the spinal canal can occur due to various degenerative changes in the surrounding soft tissues or bones. Yet there is inadequate information about their contribution to the development of spinal stenosis.

The objective of our research was to clarify the association and relative contribution of degenerative changes in tissues bordering the spinal canal, specifically facet joint hypertrophy and disc bulging, to lumbar spinal stenosis prevalence and severity. We assessed these changes on clinical images (MRI) of the low back using established measurement techniques and grading criteria in a sample of 197 adult males. From the results, posterior disc bulging appears to play a more significant role in stenosis than facet joint hypertrophy. However, degenerative findings in both structures explained little of the presence and severity of stenosis, suggesting other factors may be of greater importance. Enhanced knowledge of the contributors to lumbar spinal canal stenosis will advance understanding of the development of the symptomatic condition of spinal stenosis and may advance our ability to work towards novel prevention and treatment strategies.

Co-authorship Statement

The study of this thesis was co-designed, analyzed, co-interpreted and written by Sujanasri Tirunagari. Dr. Michele Crites Battié conceptualized the study and contributed to study design and planning, the provision of data, and interpretation of results, and provided feedback and revision for Chapters 1-4. The study involved secondary data analysis using data from the Twin Spine Study, with the addition of dural sac cross-sectional area measurements obtained by Sujanasri Tirunagari and facet joint hypertrophy assessments by Dr. Peter Lynch, who also provided training and consultation on MRI interpretation. Dr. Kevin Gill conducted the qualitative lumbar spinal stenosis and disc bulging assessments, and Dr. Laura Gibbons provided statistical consultation.

Table of Contents

List of tables

List of figures

Chapter 1

1 Background

Lumbar spinal stenosis (LSS) is a narrowing of the spinal canal or neural foramina resulting in encroachment on the neurovascular tissues contained within. The clinical symptoms of LSS include low back pain with or without radiating pain to the lower limbs, lower limb numbness, and intermittent neurogenic claudication precipitated by walking or standing. Patients with symptomatic LSS generally demonstrate walking intolerance, pain, and disability in daily activities, and substantially lower health-related quality of life compared with healthy individuals.[1] LSS is a common source of pain and disability among older adults and is the most common reason for spinal surgery in individuals older than 65 years of age.[2]

It is recognized that spinal stenosis (narrowing) by itself does not always lead to the clinical syndrome of LSS, but the pathoanatomical feature is a prerequisite of the clinical syndrome. Yet, little is known about variations in the degenerative changes and morphology of the various structures contributing to LSS or how they relate to the development of symptoms. Such information is important to improving knowledge of the pathoanatomy and pathogenesis of spinal stenosis, and its association with symptoms. We aim to enhance knowledge of the contribution of hypertrophic and degenerative changes in the various tissues bordering the spinal canal to lumbar spinal stenosis.

1.1 Early Observation and Classification of LSS

Verbiest has been credited with bringing the condition of LSS to light in the early 1950s, describing spinal stenosis as a condition of "narrowing of a duct or channel (caused by changes in its walls, involving in one way or another, the entire duct or channel)…," which can result in compression of fixed living matter, along with disturbance of blood circulation or cerebrospinal fluid as secondary effects. Later, lumbar vertebral canal stenosis was described as a form of compressive stenosis, with compression produced by the encroachment of the surrounding structures of the vertebral canal, such as discs, ligaments, bones, etc. resulting in canal narrowing.[3]

Based on observation, Verbiest also proposed a classification of congenital stenosis as an abnormally narrow vertebral canal due to congenital malformation of the lumbar spine and developmental stenosis as genetic disturbances of both fetal and postnatal development of the lumbar vertebrae until maturity. The term acquired stenosis was proposed for narrowing of the vertebral canal entirely due to postnatal degenerative disease, spondylolisthesis, traumatic changes, bone disease, etc.[3] The latter is also often referred to as degenerative stenosis.

For diagnosing the severity of the stenosis, standardized measurements of the lumbar vertebral canal are required. Verbiest introduced the concepts of relative and absolute stenosis to address the severity of central canal stenosis. The selected threshold measurement for "relative stenosis" was determined by interpedicular midsagittal diameter measurements between 10 and 12mm; whereas "absolute stenosis" was determined by a midsagittal diameter of less than 10mm. Verbiest considered a clinical finding of absolute stenosis from a disc protrusion as an indication for surgical decompression, whereas findings of relative stenosis were viewed as a possible warning for the development of disturbances from spondylosis in the future.[3] Today it is generally accepted that disc degeneration, facet joint, and ligamentum flavum hypertrophy can all contribute to degenerative spinal stenosis.[4] However, their relative contribution is unknown.

1.2 Overview of Dural sac CSA measurements using MRI

Currently, MRI is the preferred imaging modality for the condition of LSS. Using MRI, stenosis is quantitatively measured from the dural sac cross-sectional area using axial T2-weighted MRI.[5] Measurements less than $100mm^2$ have been used to represent relative stenosis and less than $75mm^2$ to represent absolute stenosis.[6] A recent study demonstrated the *effects of slice orientation* by comparing dural sac cross-sectional area measurements obtained from routinely acquired clinical MR axial images to 3D reconstructed images oriented perpendicular to the spinal canal at the mid disc for the assessment of spinal stenosis. The impact of slice orientation on the determination of LSS was considered using a threshold of dural sac cross-sectional area of $<75mm^2$. Using a sample of 390 patients determined to have some aspect of anatomical spinal stenosis on clinical MRI, no statistically significant difference in the dural sac CSA measurements was found at the L2/3 and

L3/4 levels. However, measurements from clinical imaging at the L4/5 and L5/S1 levels without adjusting for lumbar lordosis may introduce measurement error (overestimation of canal size).[6]

1.3 Prevalence of LSS and the association of radiographic and symptomatic LSS

Kalichman et al described the prevalence of congenital and acquired or degenerative lumbar spinal stenosis and their association with LBP in a community-based sample of 191 participants (32-79 years old) consecutively enrolled from 3,590 participants aged 40 to 80 years for an ancillary project of the Framingham Heart Study. The participants had undergone multidetector CT scanning for the abdomen and chest to assess coronary and aortic calcification. Later the 8 slices of the multidetector CT scans were used to evaluate lumbar stenosis using axial plane measurements for acquired (soft-tissue windows) and congenital lumbar stenosis (bone windows). The anteroposterior diameter of the spinal canal was measured at the mid vertebral body level to identify congenital stenosis and at the intervertebral disc level as an indicator of acquired stenosis. Kalichman et al found that the prevalence of congenital LSS was 4.7% for relative and 2.6% for absolute, whereas the prevalence of acquired stenosis was 22.5% for relative stenosis and 7.3% for absolute stenosis for the age group less than 40 years, and increased with age to 47.2% and 19.4%, respectively, among the age group of 60-69 years.[7] Further analysis revealed a significant association of absolute LSS with LBP, however, age, sex, BMI, and relative LSS was not significantly associated with LBP.[7]

Patients with spinal stenosis apparent on imaging do not necessarily exhibit symptoms. Maeda et al. examined radiographic LSS and investigated factors (peripheral artery disease and diabetes mellitus) associated with symptomatic LSS. This evaluation was done in 968 participants (men, 319; women, 649) ranging in age from 21-93 (mean age 66.3) years, of the population-based Wakayama spine study. Participants underwent a sagittal T2 weighted total spinal MRI in a supine position on the same day as a physical examination. The inclusion criteria for the diagnosis of symptomatic LSS were pain, numbness, and/or fatigue in buttocks, and lower extremities with or without LBP, the presence of intermittent claudication, provoked symptoms due to walking and standing. Those with a history of lumbar surgery for symptomatic LSS were excluded.

Radiographic LSS was graded qualitatively by an orthopedic surgeon using axial images and Suri's classification[8] scheme (Grade 0, no narrowing; Grade 1, mild: narrowing of <one-third of the normal area; Grade 2, moderate: narrowing of one-third to two-thirds of the normal area; Grade 3, severe: narrowing of > two-thirds of the normal area). The study findings revealed the presence of symptomatic LSS in 92 (9.5%) participants, including 32 (10%) men and 60 (9.2%) women and the prevalence rate of diabetes mellitus and peripheral artery disease was 8.4% and 1.86%, respectively. Significant correlations were found with symptomatic LSS for age, Ankle-brachial Index (ABI), Peripheral artery disease (PAD), and the most severe radiological LSS grades on MRIs.[1]

1.4 Location of LSS in patients with the clinical syndrome

LSS is often characterized by the anatomical site of narrowing, including the central canal, lateral recess or foramina, or both (mixed stenosis). This differentiation is important in clinical practice as symptoms and treatment may vary depending on location. Central and lateral stenosis have been observed at every lumbar level on clinical imaging.[9] According to a study of the radiological reports of 173 patients diagnosed with the clinical syndrome of LSS, stenosis was reported in 93.1% at L4/5, followed by 65.9% at L3/4, 49% at L5/S1, 34% at L2/3, and 11.6% at L1/2, and was present at multiple levels in most subjects (79.2%). The majority (68.2%) also had findings of both central and lateral stenosis. When both types of stenosis were present, central stenosis was typically the most severe, except at the L5/S1 level, where the more severe finding was most often lateral stenosis. In the 33 (19.1%) who had *central stenosis only*, of any severity level, the findings were most commonly at L4/5 (48.5%) and L3/4 (28.8%), whereas in the 22 (13%) who had *lateral stenosis only*, of any severity level, the findings were most common at L4/5 (46%), followed by L5/S1 (32.4%), with 89.2% of findings present bilaterally.[9] This study's findings were similar to other studies looking at the prevalence of imaging findings of stenosis in patients with the clinical diagnosis.[10,11] In earlier studies, however, there is a disparity in the prevalence of mixed stenosis, which may be due to considerations of severity. Two studies that adhered to a strict level of severity for reported radiological findings found a lower prevalence of mixed stenosis (9–35%),[12,13] while studies reporting a higher prevalence of mixed stenosis (59–69%) included all imaging findings of

stenosis regardless of severity.[14,8] Tomkins-Lane et al's findings shed light on this disparity. When they considered only moderate to severe levels of radiological stenosis, central stenosis was found to be most prevalent (46.2%), with mixed stenosis accounting for only 30.8% of cases. When mild radiologically stenotic levels were also considered with at least one moderate to severe finding, only 17.9% were found to have central stenosis alone and mixed stenosis doubled to 59.0%.[9]

1.5 Pathoanatomical contributors of LSS

Today, LSS is viewed as a primarily age-related condition mainly caused by degenerative changes and hypertrophy of the intervertebral discs, ligamentum flavum,[15,16] and facet joints, resulting in pressure on the neurovascular contents of the central spinal canal and foramina. Yet, the relative contribution of morphological variations in each of these structures to LSS is unknown. Such information would be important to improving knowledge of the pathoanatomy and pathogenesis of LSS. Furthermore, related LSS phenotypes may be recognized with implications to etiognosis and prognosis.

An accurate measurement of the morphology of the contributing structures is needed to understand the contribution of each to LSS.

1.5.1 Ligamentum flavum hypertrophy

Most researchers describe the ligamentum flavum (LF) in histological, biochemical, or biomechanical terms.[16,17] A recent study has standardized a measurement technique for ligamentum flavum morphology specifically related to ligament thickness.[17] In a sample size of 214 patients suffering from back pain for more than 12 weeks, higher Pfirrmann (disc degeneration) grade, decreased anterior disc height, and facet tropism were associated with ligamentum flavum thickness at different levels of the lumbar spine. It was postulated that greater disc degeneration (Pfirrmann grade) and decreased anterior disc height may lead to ligamentum flavum hypertrophy due to ligament buckling at L1 to L5, whereas facet tropism may lead to ligamentum flavum hypertrophy at L5/S1.[18] In a study of 419 patients, MRI scans with clinical symptoms related to the spine, spinal cord, and cauda equina were assessed to investigate the

association of LF hypertrophy pathogenesis and mechanical stress, and the relation between segmental instability, disc degeneration, and facet joint osteoarthritis at the L4-5 spinal level. The analysis concluded that LF thickness was significantly correlated with age, vacuum phenomenon, increased disc degeneration severity (using Pfirmann's criteria), and facet joint osteoarthritis.[19]

1.5.2 Facet joint orientation and hypertrophy

Studies have been conducted on facet joint hypertrophy, revealing no association between facet joint osteoarthritis and LBP while adjusting for sex, age, and BMI.[20,21] Other studies found no statistically significant correlation between asymmetry of the facet joints and the presence of disc degeneration at any spinal level.[22,23] A study considered the association of biomechanical changes of facet joints (orientation and morphology) relative to isthmic spondylolysis. This study concluded that the patients with frontally oriented facet joints at the L5-S1 level had a high incidence of developing isthmic spondylolysis when lumbar vertebra incorporated with facet tropism.[24,25] Another study observed that the patients with sagittally oriented facet joints at the L4/5 level had a high incidence of developing degenerative spondylolisthesis when compared to the normal group.[26,25] Greater LF thickness was associated with sagittal facet orientation and facet osteoarthritis.[19] Another study assessed the correlation between lumbar intervertebral disc degeneration and facet joint degeneration and analyzed the risk factors for lumbar degeneration at L3 through S1 spinal level using MRI and CT scans of 152 patients. There was a significant decrease in the intervertebral disc height (graded using Pfirrmann criteria) with increased facet joint degeneration grade (graded using Weishaup criteria). Left and right facet joint osteoarthritis was significantly increased with increased disc degeneration grade.[28] Recently, Akar and Somay compared morphometric features (facet joint angle, facet tropism, ligamentum flavum hypertrophy, transverse spinal canal diameter, and lateral recess height) in congenital and acquired spinal stenosis patients and concluded no significant difference in measurements between the groups.[27] Furthermore, Sang et.al investigated the association between superior articular process CSA with lumbar central canal spinal stenosis in 109 patients with a mean age of 70.81±6.94 (range 60–88 years). They concluded that superior articular process CSA was greater in the

patients with LSS (mean CSA= 123.59±14.18 mm^2) than in the control group (mean CSA 96.63±13.37 mm^2) .[29]

From the review of literature, there is no clear association of lumbar spinal facet joint osteoarthritis with low back pain.[18] With respect to biomechanical findings, sagittal facet joint orientation was mainly present in degenerative spondylolisthesis, whereas coronal/frontal facet orientation was associated with isthmic spondylolisthesis.[25]

1.5.3 Intervertebral disc degeneration

Degenerative changes of the intervertebral disc are also thought to play an important role in lumbar spinal stenosis, and they have been shown to largely share additive genetic influences.[10] A study that analyzed the relationship between facet tropism and disc degeneration in 46 subjects found a significantly higher prevalence of disc degeneration at L3 through S1 spinal levels. However, the magnitude of facet angle was not statistically significant with the presence of disc degeneration,[22] and degenerative or isthmic lumbar spondylolisthesis.[25,26,27] A study of 419 patients with clinical symptoms related to the spine, spinal cord, and cauda equina investigated the association between age and disc degeneration (graded using Pfirmann's criteria), and facet joint osteoarthritis at the L4/L5 spinal level. Age was statistically significantly correlated with disc degeneration and facet osteoarthritis.[30] Another study by Song et al assessed the correlation between lumbar vertebral disc and facet joint degeneration and analyzed the risk factors for lumbar degeneration at the L3 through S1 spinal levels using MRI and CT scans of 152 patients. The study findings concluded that there was a significant increase in facet joint arthritis grade (Weishaup grading criteria) with increased disc degeneration grade (Pfirrmann criteria).[31] The presence of facet tropism increases the risk of disc degeneration.[22] However, the specific mechanisms or aspects of disc degeneration behind this association need further study.[32]

To summarize, the findings from the literature show that there is a significant association between ligamentum flavum hypertrophy, facet joint hypertrophy, and disc degeneration, but their associations with LSS were inconsistent. In the case of facet joint hypertrophy, when measured qualitatively, there was no association with LSS, but in another study, facet joint cross-sectional

area was associated with LSS, suggesting measurement may be an issue. We are aware of no study that specifically investigated the contribution of intervertebral disc degeneration and facet joint arthropathy to lumbar spinal stenosis in the general population. We aim to enhance knowledge of the contribution of each of these structures surrounding the lumbar vertebral canal to LSS in the general adult male population using previously standardized measurements and methods.

Chapter 2

2 Methodology

The objective of the proposed study was to investigate the association and relative contribution of facet joint hypertrophy and disc degeneration, particularly disc bulging, with dural sac cross-sectional area and the prevalence and severity of (radiographic) lumbar central canal stenosis in a general adult male population.

2.1 Study Sample

The study utilized the imaging data from the population-based Twin Spine Study, including 15-year follow-up data collected between 2007 and 2008.[11] The subjects came from a total of 600 twins (300 pairs) originally recruited from the population-based Finnish Twin Cohort with 13,888 male pairs born before 1958.[33]

The Twin Spine Study participants were recruited in two waves of data collection in 1991-92 and 1996-97. The initial selection of 117 pairs of MZ twins in the original study was based solely on the discordance between twin siblings for a specific common behavioral or environmental factor (e.g., sedentary or heavy occupational physical demands, routine exercise participation, or occupational driving),[34] based on surveys conducted in 1975 and 1981.[33] They were found to be quite representative of the Finnish Twin Cohort, which was representative of the Finnish population.[34] In the later wave, an additional random sample of 30 MZ pairs, stratified by age, was added to the sample, as were 153 pairs of DZ twins selected using analogous criteria as the MZ twins, yielding a total sample of 600 subjects.[33]

The follow-up Twin Spine Study subjects included in the present study comprised 152 monozygotic (MZ) and 51 dizygotic (DZ) male twin subjects yielding a total sample of 203 subjects The MZ twins participated in the follow-up approximately 15 years after the initial data collection, and the DZ twins approximately 10 years after initial recruitment, who were still living and able to travel to the data collection site in central Finland All study subjects from the follow-up with available MRI images were included, except cases with prior lumbar spine surgery, severe scoliosis, or poor image quality, such that the study measurements could not be obtained.

The present study was approved by Western University Research Ethics Board at the University of Western Ontario.

2.2 Data Acquisition

Data acquisition in the original study involved transporting twins from all parts of Finland to a central location where a team of project investigators, technicians, and other staff conducted structured interviews, including demographic information and health history. Physical examinations and clinical testing, including lumbar MRI scanning and anthropometric measurements over two days for each twin pair. [35]

2.2.1 MRI protocol

All study subjects traveled to an imaging center in central Finland for 15-year follow-up lumbar spine magnetic resonance imaging (MRI) between 2007 and 2008. Images were obtained by Siemens Zebra scanner ("Avanto" with software MR B15, Siemens AG Erlangen, Germany) using specific protocols for sagittal and axial images of the lumbar spine from L2-3 through L5/S1. T2-weighted images were obtained with repetition and echo times of 2450 and 90, respectively. The field of view was 320 mm (in axial, 348×384 mm) and the pixel size was 0.8125 mm. The slice thickness and interslice gap were 4 mm and 0.4 mm, respectively, for the sagittal images and 3 mm and 0.3 mm for axial slices. [11,36]

2.2.2 Assessment of facet joint hypertrophy

Qualitative measurements of facet joint osteoarthritis of all subjects' axial MR images of the lower four lumbar levels were graded by a radiologist using previously described criteria by Weishaup et al.[37] Each facet joint was characterized into one of 4 grades (Table 1, Figures 1-4).

Facet joint arthritis or hypertrophy was qualitatively graded by a radiologist using axial T2 weighted lumbar spine MR images at the mid intervertebral disc level at the L2-3, L3-4, L4-5, and L5/S1 discs. To determine intra-rater reliability, 30 subjects' image sets were randomly selected, and repeated measurements were obtained with a two-week interval, with measurements blinded to all previous measurements. The weighted Kappa (w2) for the intra-observer reliability of the measurements, as determined using blinded, repeated measurements of a sample of 30 subjects' images by the radiologist was 0.75 overall.

Table 1: Facet joint hypertrophy grading system by Weishaup et al.[37]

Grade	Criteria
0	Normal facet joint space (2±4 mm width)
1	Narrowing of the facet joint space (< 2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process
2	Narrowing of the facet joint space and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions
3	Narrowing of the facet joint space and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts

Example figures for facet joint grading criteria:

Figure 1: Facet joint grade 0

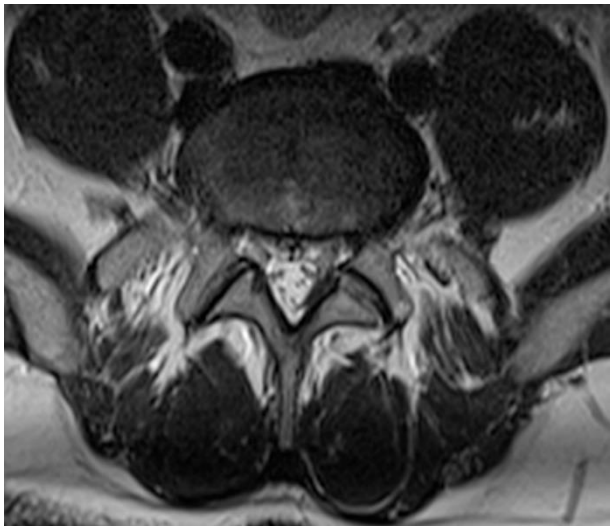


Figure 2: Facet joint grade 1

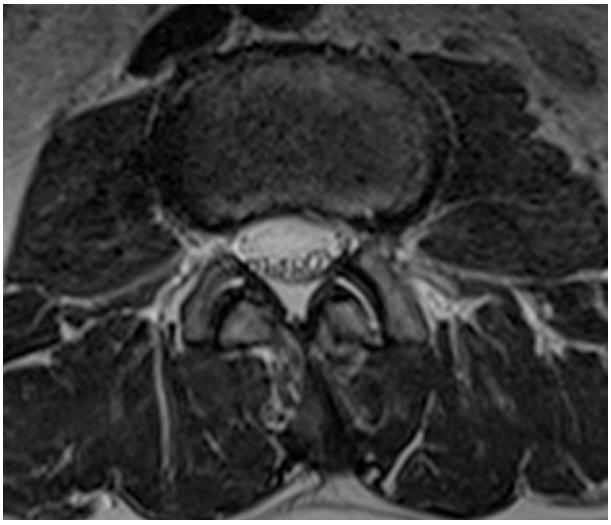


Figure 3: Facet joint grade 2

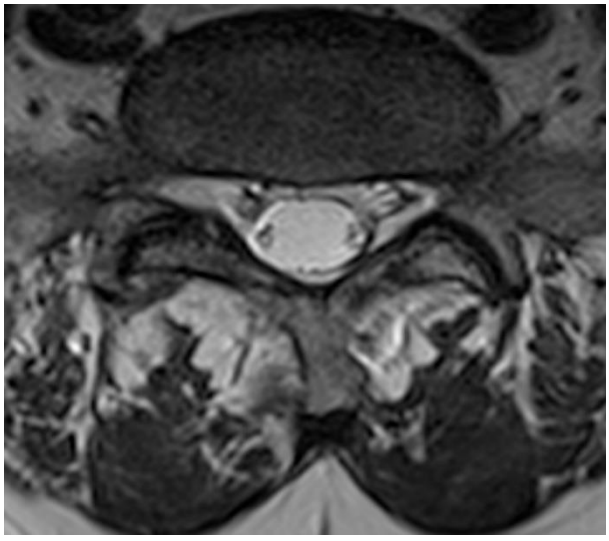
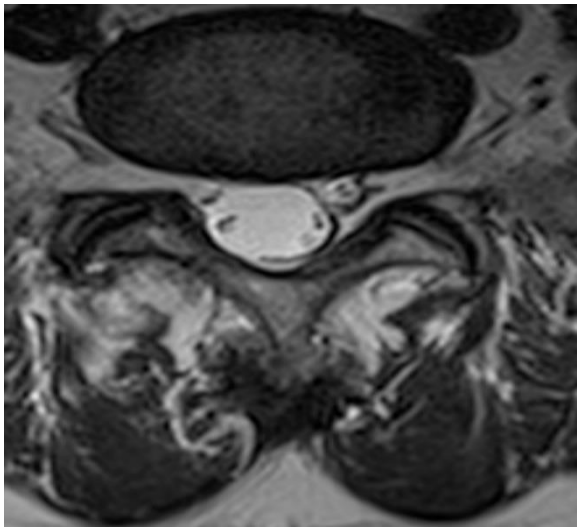


Figure 4: Facet joint grade 3



2.2.3 Assessment of intervertebral disc degeneration

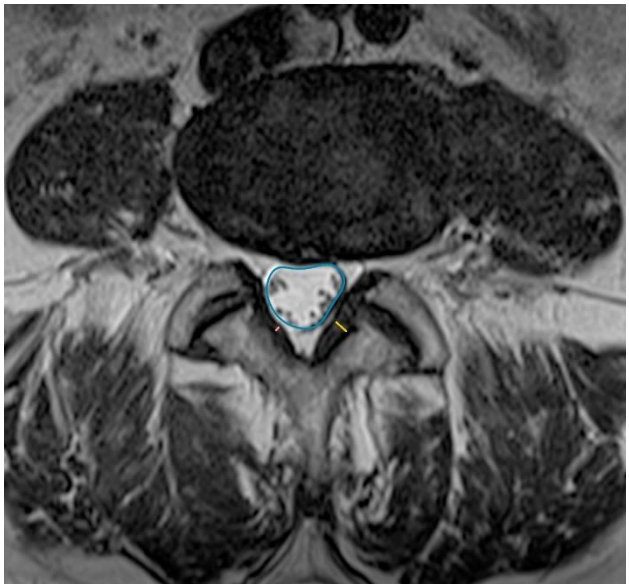
Qualitative measurements of intervertebral disc degeneration were previously conducted by an experienced spine surgeon. Each spinal level, L1-L2 through L5/S1, was evaluated for disc narrowing and posterior disc bulging using a 4-grade scale (0-normal, and 1 to 3 representing progressive degrees of narrowing or bulging). Blinded, repeated measurements on a randomly selected sample of 75 of the study MRI were conducted to assess intra-rater reliability. Intraclass correlation coefficients for intra-rater reliability were 0.78 for disc height for the upper lumbar levels, 0.77 for the lower lumbar levels, and 0.67 and 0.59 for posterior disc bulging for the upper lumbar and lower lumbar levels, respectively.

2.2.4 Assessment of lumbar spinal stenosis

Anatomical assessment of lumbar central canal stenosis was conducted both qualitatively and quantitatively at the intervertebral disc level. The quantitative measures were acquired dimensions of central canal capacity, and the presence of stenosis was determined based on these dimensions.

Quantitative measurements of Dural Sac CSA at mid disc level at the L2-3, L3-4, L4-5, and L5-S1 discs from axial T2-weighted images were obtained to analyze the canal capacity and degenerative or central canal LSS. The dural sac cross-sectional area was measured starting at the posterior border of the ligamentum flavum on each side through the posterior border of the disc. The segmentation or tracing of all images to acquire the quantitative measurements was conducted by one observer. The intra-class correlation coefficient for the intra-rater reliability determined from blinded, repeated segmentation of a randomly selected set of 30 subjects' images was 0.94(95% CI 0.88-0.97) for L2-3, 0.94(95% CI 0.88-0.97) for L3-4, 0.91(95% CI 0.82-0.95) for L4-5, and 0.83(95% CI 0.68-0.91) for L5- S1 dural sac cross-sectional area. The measurement technique is shown in Figure 5.

Figure 5: Measurement of dural sac CSA



Qualitative assessments of all subjects' MR images were performed by an experienced orthopedic spine surgeon blinded to twinship, environmental exposures, and symptom history. The central canal at each lumbar disc level from L2-3 through L5/S1 was rated on a scale from 0-3, with 0 representing no stenosis, 1=mild (compromise $\leq$1/3 of the normal size), 2=moderate (compromise between 1/3-2/3 of the normal size), and 3=severe (compromise >2/3 of the normal size). The intra-class correlation coefficient for the intra-observer reliability of the measurements, as determined using blinded, repeated measurements of a sample of 75 subjects' images by the spine surgeon, was 0.85 (95%CI: 0.77- 0.90) for L2-L4 and 0.70 (95%CI: 0.57-0.80) for L4-S1.

2.3 Data Analysis

We examined the distribution of the variables of interest and characterized the sample using descriptive statistics. We used mean and standard deviations for dural sac cross-sectional area (continuous variables), age and BMI, and frequencies and percentages for facet joint hypertrophy, presence or categorization of LSS, and lumbar disc degeneration. Outliers were identified for quantitative measures (e.g. dural sac cross-sectional area) using box plots. All statistical analyses were performed using Stata/IC 16.1 for Mac (Intel 64-bit), TX, USA software.

The association of facet joint arthropathy and disc degeneration with dural sac cross-sectional area, LSS occurrence, and severity, as well as their relative contribution to LSS, were of interest. To examine the association of the degenerative or pathoanatomical features of the disc and facet joints with the dependent variable of dural sac cross-sectional area (a continuous variable), we used univariate and multivariable linear regression. The association with categorical dependent variables (presence of LSS, e.g., relative/absolute stenosis, or moderate/severe LSS) was examined using univariate and multivariable logistic regression. The relative and total contribution of the degenerative or pathoanatomical factors to the dural sac cross-sectional area were conveyed in variance explained (R^2) and odds ratios in the univariate and multivariable models.

Chapter 3

3 Results

Of the study sample comprising 203 men, there were missing images or assessments for five subjects, leaving 198 subjects. The mean age of the sample was 61±7.5 years of age, with a range from 50 to 79 years. The mean BMI was 26.5±3.4. One subject was subsequently excluded as an extreme outlier, resulting in 197 observations for analysis purposes.

Facet joint hypertrophy and posterior disc bulging were graded at the four lower lumbar disc levels, with moderate-severe degeneration of facet joints most commonly observed at L3/4 (29.8%) and L4/5 (27.7%). In contrast, severe posterior disc bulging was very uncommon across the lumbar spine, with 1.0% or less of the discs at each lumbar level being rated as having severe posterior bulging (Table 2).

Dural sac cross-sectional area (mm^2) measured at the four lowest lumbar disc levels was similar at L3/4 and L4/5, and largest at L2/3. The highest prevalence of relative (<100mm^2) and absolute stenosis (<75mm^2) was 14.1% and 6.5%, respectively, at the L5/S1 level, and the lowest prevalence of 2.0% and 1.5% were found at L2/3. For qualitatively assessed LSS, moderate and

severe central canal stenosis were most commonly observed at L3/4 and L4/5. At both levels, 11.6% and 15.6% respectively were rated as being moderately stenotic and 1.5% as being severely stenotic (Table 3).

The association of facet joint hypertrophy and disc bulging with LSS by spinal level

In the study sample, there were limited observations of qualitatively and quantitatively assessed severe or absolute stenosis, such that it was not possible to preserve all three grades (mild, moderate, and severe) in analyses of the association of facet joint hypertrophy and disc degeneration with LSS by spinal level. Thus, we dichotomized qualitatively assessed LSS by combining mild, moderate, and severe grades as "present" versus "normal or absent", and disc bulging was dichotomized similarly. Quantitatively assessed LSS was dichotomized as the absence versus the presence of relative or absolute stenosis ($<100mm^2$). Mean right and left facet joint hypertrophy was dichotomized as normal/mild (<1.5) versus moderate/severe (≥1.5).

We used simple linear regression to investigate the association of mean (right and left) facet joint hypertrophy and posterior disc bulging with spinal canal capacity, represented by dural sac cross-sectional area (mm^2), by spinal level. Mean facet joint hypertrophy explained 8.3% ($p<0.001$) of the total variance in canal capacity at the L2/3 level but was not statistically significantly associated with canal capacity at the other levels studied. Posterior disc bulging explained 3.0% of the total variance in spinal canal capacity at L3/4 ($p=0.01$), the only level for which a statistically significant association was found (Table 4). Unsurprisingly, similar to the univariate analyses, the multivariable model including both facet joint hypertrophy and posterior disc bulging explained about 8.0% of the total variance in spinal canal capacity at L2/3.

We used univariate logistic regression to investigate the association between mean facet joint hypertrophy (normal/mild versus moderate/severe) and posterior disc bulging (absent versus present) with relative or absolute LSS ($<100mm^2$). Mean facet joint hypertrophy was statistically significantly associated with the presence of relative or absolute stenosis only at L2/3 (OR=4.2), and posterior disc bulging was associated with quantitatively assessed stenosis only at L3/4 (OR=4.3, Table 5).

Also using univariate logistic regression, mean moderate/severe facet joint hypertrophy was statistically significantly associated with qualitatively assessed LSS at L2/3 only, and presence of posterior disc bulging was associated with qualitatively assessed LSS at all levels examined (L5/S1 was omitted due to too few observations of LSS, Table 6). We could not use a multivariable model to investigate the association of the mean (right and left) facet joint hypertrophy and posterior disc bulging with relative or absolute LSS (dural sac cross-sectional area <100mm^2) and qualitatively assessed LSS by spinal level because of too few observations.

The association of facet joint hypertrophy and disc bulging with LSS when combining L3/4 and L4/5 spinal levels

Because of the low frequency of qualitatively assessed moderate and severe stenosis and quantitatively assessed absolute stenosis at each spinal level and considering the similar canal dimensions of the most commonly affected spinal levels, L3/4 and L4/5, stenosis at either level was considered for analysis. Thus, the L3/4 spinal level was substituted for L4/5, only when there was stenosis at L3/4 and none at L4/5. The mean facet joint hypertrophy and posterior disc bulging were from the corresponding spinal level.

For the combined level analyses, the dichotomized variables of both qualitatively and quantitatively assessed LSS were used, however, the independent variables of mean facet joint hypertrophy and posterior disc bulging retained their original ordinal grades (0-3). The prevalence of relative LSS for combined levels was 20.8% and for absolute LSS was 6.6%, where the prevalence of qualitatively assessed LSS for combined levels was 62.9%.

We used simple linear regression to investigate the association of mean (right and left) facet joint hypertrophy and posterior disc bulging with spinal canal capacity, represented by dural sac cross-sectional area (mm^2) of the combined levels. The mean facet joint hypertrophy explained 2.6% (p-value 0.01) and posterior disc bulging explained 6.0% (p-value 0.001) of the total variance in canal capacity. The multivariable model, including mean facet joint hypertrophy and posterior disc bulging, explained 8.0% of the total variance in the canal capacity. Using univariate logistic regression, mean facet joint hypertrophy and posterior disc bulging were not statistically significantly associated with relative or absolute LSS. Facet joint hypertrophy was not associated

with qualitatively assessed LSS. However, posterior disc bulging was statistically significantly associated with the presence of qualitatively assessed LSS with an odds ratio of 2.3 (Table 7).

Chapter 4

4 Discussion

In a general population sample of older men, we found that facet joint hypertrophy and posterior disc bulging were inconsistently associated with central canal stenosis when analyzed by spinal level, except for a consistent association of posterior disc bulging with qualitatively assessed LSS across all levels. Posterior disc bulging was also associated with both reduced canal capacity and qualitatively assessed central canal stenosis when considering the combined levels of L3/4 and L4/5. Except for L5/S1, the prevalence of quantitatively determined relative or absolute LSS was very similar to qualitatively assessed moderate or severe LSS. The prevalence of relative stenosis was 14.1% in the study sample and absolute stenosis was 6.5% at the L5/S1 level, whereas no qualitatively assessed severe LSS was reported at L5/S1. Except for the L5/S1 level, this finding was in line with Mannion et al study, where the dural sac cross-sectional area measurements and qualitatively assessed LSS delivered similar findings and were strongly correlated.[38]

Regarding the presence of LSS in the general population, Kalichman et al reported a prevalence rate of 22.5% for relative stenosis and 7.3% for absolute stenosis in the lumbar spines of a subgroup of participants with a mean age of 52.6±10.8 from the Framingham Study. This prevalence rate could differ because of the different definition of LSS used or the different imaging modality used (CT scan). They measured anteroposterior dural sac CSA of <12mm as relative stenosis and <10mm as absolute stenosis from L2/S1 levels using CT scans, whereas, we measured the dural sac cross-sectional area of <100mm^2 as relative and <75mm^2 as absolute stenosis.[7] Eun et al concluded that the spinal canal area was more narrowed on CT scans than on MRI which results in high prevalence.[39] For canal capacity, as expected, the measurements obtained in the present study were similar to those reported of the larger Twin Spine Cohort obtained 10-15 years earlier.[10]

The prevalence of LSS in a general population sample was reported in another study, the Wakayama study from Japan. In their sample of 938 participants with a mean age of 67.3 years, the prevalence rate of qualitatively assessed severe LSS at L3/4 was 16.1% and L4/5 was 23.9%, whereas the prevalence in the current study was 1.5% at both levels. The Wakayama study reported a prevalence of severe stenosis of 6.1% at L2/3 and 3.4% at L5/S1, whereas there was no severe stenosis observed at these levels in the present study.[40] This disparity in LSS prevalence despite similar qualitatively graded criteria is not easily explained, but may be due, in part, to differences in Finnish and Japanese study populations.

In the current study, facet joint hypertrophy was statistically significantly associated with both canal capacity and LSS only at L2/3 but was not at the L3/4, L4/5 and L5/S1 levels. This finding may be explained, in part, by study findings from Barry and Livesley, who measured the cross-sectional area of facet joints in both patients who have normal facet joints and disc degeneration and patients with degenerated facet joints and normal discs. They found no significant difference in the size of the facet joints between the groups.[41] In line with these findings, another study measured the facet joint thickness and area as facet joint degeneration in patients with stenosis and controls (without symptoms) at the L4/5 level and found the thickness and area of the joint were smaller in the stenosis patients than in controls, although this was not statistically significant.[42]

Our finding of posterior disc bulging associated with qualitatively assessed LSS at all levels examined supports the general view that disc degeneration contributes to LSS. An earlier study utilizing the complete Twin Spine Study Cohort (n=600) to estimate the magnitude of genetic versus environmental influences on central canal stenosis also supported a link between disc bulging and central canal stenosis through shared genetic influences.[10] To our knowledge, we are aware of no other studies looking specifically at the association of LSS and disc degeneration.

The inconsistent or modest associations of facet joint hypertrophy and posterior disc bulging with central canal stenosis, suggest that other factors may be primarily responsible for the occurrence of LSS. One possibility is that abnormal development of the bony canal (congenital stenosis) could play a larger role in degenerative LSS than previously thought, with mild degeneration of soft

tissue structures around the spinal canal leading to stenosis. This was concluded by Soldatos et al who measured the presence and absence of disc degeneration, epidural lipomatosis, Schmorl's nodes, spondylolisthesis, pars defects, and stress reactions of the posterior vertebral elements in patients with congenital stenosis and control group (canal diameter ≥14mm). Their findings suggested that subjects with congenital stenosis have a higher incidence of degenerative changes and soft tissue elements encroaching on the lumbar spine.[44]

To our knowledge, this is the only study that has investigated the contribution of pathoanatomical findings in the facet joints and discs to quantitatively and qualitatively assessed LSS in the general population. However, there are some limitations of the present study that must be noted. First, there are limitations related to the measurements, particularly the qualitative assessments of facet joint hypertrophy, posterior disc bulging, and lumbar spinal stenosis, as each has suboptimal reliability. This may likely lead to some degree of misclassification that would tend to dilute associations. Also, the degeneration or hypertrophy of each pathoanatomical structure was measured by a single rater. Second, due to the low prevalence of quantitatively assessed relative and absolute or qualitatively assessed moderate and severe stenosis by spinal level, we had to dichotomize variables, and information was lost on the severity of facet joint hypertrophy, posterior disc bulging, and LSS in related analyses, which also may have diluted associations. A final consideration is that all of our participants were white, Finnish males. Thus, the results of this study may not be representative of other races and ethnicities or females.

In conclusion, associations of facet joint hypertrophy and posterior disc bulging with LSS were inconsistent across lumbar spinal levels and the different LSS phenotypes, except for posterior disc bulging that was consistently associated with qualitatively assessed LSS across the lumbar levels assessed. For this LSS phenotype, it would appear that posterior disc bulging plays a more significant role in stenosis than facet joint hypertrophy. However, both the structures explained little of the variance in canal capacity or the odds of having stenosis. Further research is needed to confirm and expand these study findings using larger samples that can support more refined measures of facet joint hypertrophy and disc degeneration and stenosis to further clarify their associations.

4.1 Clinical Implications

LSS is a common cause of pain and disability in older adults. As the pathoanatomical feature of stenosis is a prerequisite for the clinical syndrome, a clear understanding of its pathoanatomy and pathogenesis is of clinical interest. Generally, LSS is viewed as a degenerative condition due to degenerative changes in the structures adjacent to the spinal canal, however, as our findings of facet joint hypertrophy and posterior disc bulging explained little of the variation in canal capacity and LSS, the explanation may not be that simple.

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Table 2: Prevalence of mean facet joint hypertrophy and posterior disc bulging categories by spinal level

N=198	**L2/3**	**L3/4**	**L4/5**	**L5/S1**
	Frequency (%)	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
Mean FJH				
Normal-mild (<1.5)	122(61.6%)	98(49.5%)	85(42.9%)	110(55.5%)
Mild-Mod (1.5)	38(19.1%)	41(20.7%)	58(29.2%)	48(24.2%)
Mod-Sev (>1.5)	38(19.1%)	59(29.8%)	55(27.7%)	40(20.0%)
Posterior Disc bulge				
Normal	92(46.5%)	69(34.8%)	47(23.7%)	33(16.6%)
Mild	87(44.0%)	103(52.0%)	107(54.0%)	131(66.1%)
Moderate	17(8.5%)	24(12.1%)	42(21.2%)	33(16.6%)
Severe	2(1.0%)	2(1.0%)	2(1.0%)	1(0.5%)

Mean FJH was graded on a 3-point scale, and posterior disc bulging was graded on a 4-point scale.

Table 3: Dural sac CSA (mm^2) and prevalence of quantitatively assessed relative and absolute LSS, and qualitatively assessed LSS by spinal level

n=198	**L2/3**	**L3/4**	**L4/5**	**L5/S1**
	M(sd)/F(%)	**M(sd)/F(%)**	**M(sd)/F(%)**	**M(sd)/F(%)**
Dural sac CSA (mm^2)	172.0(40.9)	151.0(44.2)	150.0(51.9)	157.0(61.8)
Relative stenosis (<100mm^2)	4(2.0%)	17(8.5%)	24(12.0%)	28(14.1%)
Absolute stenosis (<75mm^2)	3(1.5%)	8(4.0%)	8(4.0%)	13(6.5%)
Qualitatively assessed LSS				
No stenosis	166(83.9%)	120(60.6%)	93(46.9%)	184(92.9%)
Mild	25(12.6%)	52(26.2%)	71(35.8%)	10(5.05%)
Moderate	7(3.5%)	23(11.6%)	31(15.6%)	4(2.0%)
Severe	-	3(1.5%)	3(1.5%)	-

Dural sac CSA: dural sac cross-sectional area in mm^2, Relative: dural sac CSA <100mm^2, Absolute: dural sac CSA <75mm^2, LSS: central canal stenosis qualitatively graded from 0-3. Bolded M(sd) represents the mean and standard deviation of the continuous variables and F (%) represents the frequencies and percentage of the categorical variables.

Table 4: Univariate linear regression analyses: Associations of spinal canal capacity (dural sac CSA (mm^2)) with mean facet joint hypertrophy and posterior disc bulging by spinal level

n=197	L2/3		L3/4		L4/5		L5/S1	
	R^2	P-value	R^2	P-value	R^2	P-value	R^2	P-value
Mean FJH	0.0826	< 0.001*	0.0137	0.10	0.0008	0.70	0.0097	0.14
	(-24.1)		(-10.2)		(-2.9)		(-12.2)	
Disc bulge	0.0164	0.07	0.0303	0.01*	0.0029	0.45	0.0076	0.34
	(-10.5)		(-15.9)		(-6.6)		(-14.4)	

Mean FJH (0-3) was dichotomized as absent/mild (<1.5) or moderate/severe (≥1.5), posterior disc bulging graded 0-3 was dichotomized as absent=0 or present= 1-3, * indicates statistical significance (P<0.05), coefficients are in parenthesis.

Table 5: Univariate logistic regression analyses: Associations of the presence of Relative or Absolute LSS with mean facet joint hypertrophy and posterior disc bulging by spinal level

n=197	L2/3		L3/4		L4/5		L5/S1	
	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value
Mean FJH	4.2	0.09*	2.7	0.05	1.8	0.16	0.9	0.66
Disc bulge	2.2	0.28	4.3	0.01*	0.9	0.86	1.0	0.95

Mean FJH (0-3) was dichotomized as absent/mild (<1.5) or moderate/severe (≥1.5), posterior disc bulging graded 0-3 was dichotomized as absent=0 or present= 1-3, * indicates statistical significance (P<0.05).

Table 6: Univariate logistic regression analyses: Associations of qualitatively assessed LSS with mean facet joint hypertrophy, and posterior disc bulging by spinal level

n=197	L2/3		L3/4		L4/5		L5/S1	
	Odds ratio	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**
Mean FJH	3.8	0.001*	1.1	0.71	1.0	0.97	1.3	0.65
Disc bulge	5.9	0.001*	3.4	<0.001*	2.8	0.004*	-	-

Mean FJH (0-3) was dichotomized as absent/mild (<1.5) or moderate/severe (≥1.5), posterior disc bulging graded 0-3 was dichotomized as absent=0 or present= 1-3, * indicates statistical significance (P<0.05).

Table 7: The association of facet joint hypertrophy and posterior disc bulging with LSS when combining L3/4 and L4/5 spinal levels

L3/4-L4/5	Canal capacity(mm^2)		Relative LSS		Absolute LSS		Qualitative LSS	
Univariate analysis	R^2	**P-value**	R^2	**P-value**	**R^2**	**P-value**	**R^2**	**P-value**
Mean FJH	0.03 (-11.5)	0.01*	1.5	0.13	1.8	0.20	1.1	0.59
Disc bulge	0.06 (-14.0)	0.002*	1.4	0.22	1.9	0.22	2.3	0.001*
Multivariate analysis	0.08							
Mean FJH	(-11.7)	0.009*						
Disc bulge	(-14.2)	0.001*						

Mean FJH (0-3) a mean value <1.5 graded as 0, 1.5=1, and >1.5=2), Posterior disc bulging was graded between 0-3, * indicates statistical significance (P<0.05), coefficients are in parenthesis.