Introducing Standing Weight-bearing MRI in the Diagnostics of Low Back Pain and Degenerative Spinal Disorders

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THE 3 ORIGINAL PAPERS ARE

1. External pneumatic compression device prevents fainting in standing weight-bearing MRI: a cohort study. Hansen BB, Bouert R, Bliddal H, Christensen R, Bendix T, Christensen A, Mehlsen J, Resti Z, Boesen M. Skeletal Radiol. 2013;42:1437-42.
2. Effect of Lumbar Disc Degeneration and Low-Back Pain on the Lumbar Lordosis in Supine and Standing: A Cross-Sectional MRI Study. Hansen BB, Bendix T, Grindsted J, Bliddal H, Christensen R, Hansen P, Riis RGC, Boesen M. Spine (Phila Pa 1976). 2015 Nov;40(21):1690-1696.
3. Reliability of Standing Weight-Bearing (0.25T) MR Imaging Findings and Positional changes in the Lumbar spine. Hansen BB, Hansen P, Christensen A, Trampedach C, Rasti Z, Bliddal H, Boesen M. M. Skeletal Radiol. 2017. (Ahead of print)

LOW BACK PAIN

Epidemiology

The lifetime prevalence of low back pain may be up to 80% in the industrialised countries and is one of the main causes of sick leave and disability pension with huge personal and socioeconomic consequences [1–3]. Low back pain causes more disability than any other condition, and a global point prevalence has been calculated at 9.4% (95% confidence interval (CI): 9.0-9.8) [3]. Some studies have found that the incidence only increases until the age of 40 years [4,5]. However, the overall prevalence of low back pain increases with age until 60–65 years of age [1,3] and, due to the demographic changes in the industrialised countries over the last decade, low back pain has received increased attention in global, regional, and national health policies [6].

Aetiology

Most studies have defined low back pain simply by the symptoms [7]. However, low back pain is characterised by a large heterogeneity including a variety of overlapping symptoms, such as sciatica, radiculopathy and neurological symptoms [7–12]. Radiculopathy ranges, with a prevalence of between 3% and 5% [13]. Most low back pain episodes are self-limiting; however, ongoing discomfort greater than three months increases the risk of a chronic condition [9]. This phenomenon is, to some extent, believed to be related to central sensitisation facilitated by fear-avoidance and/or bio-psycho-social factors [11,14–16]. There seems to be a growing understanding that low back pain is multifactorial. Despite this, low back pain may still be defined as *mechanical, non-mechanical, or visceral,* based on its underlying cause of pain [17,18]. (**Table 1**)

The term “mechanical low back pain” is often used as an umbrella term to define an anatomical or functional abnormality without an underlying malignant, neoplastic, or inflammatory disease [12]. Approximately 2% of mechanical low back or leg pain is accounted for by spondylolysis, internal disc disruption or discogenic low back pain, and presumed instability. The most frequent case is lumbar strain or sprain, which may also be termed “nonspecific low back pain” (>70%) [12]. “Idiopathic low back pain” may be a preferable term as it defines patients with no pathoanatomical confirmation [19]. To complicate the matter, several studies have indicated an association between Modic changes and low back pain. Modic changes are visible on conventional Magnetic Resonance Imaging (MRI), and three types have been identified (Type 1, 2, and 3) [20,21]. According to Modic et al., type 1 changes are believed to be part of the degenerative process and reflect a hypervascularity of the vertebral body secondary to inflammation [20,22,23]. It is believed that various cytokines (e.g. TNF-α, interleukin (IL)-1, IL-6, prostaglandin E2 and nitric oxide) are involved and contribute to the back pain [24–26]. Furthermore, several studies indicate that inflammation increases pressure-sensitivity in the nerve roots, which may cause radicular pain to the legs [26–28]. Despite this, the treatment effect of anti-TNF-α and anti-inflammatory agents seems moderate [29,30]. Recent studies have also indicated an association between Modic changes and a low virulence anaerobic infection [31–33].

Degenerative changes in the disc

The lumbar intervertebral disc undergoes degenerative morphological and cellular changes with age [23,34].

Table 1
Differential diagnosis of low back pain based on Jarvik and Deyo [18]

Mechanical back pain (97%)	Non-mechanical back pain (1%)	Visceral Disease (2%)
Lumbar strain or sprain Degeneration of disc and facets Herniated disc Spinal stenosis Osteoporotic compression fracture Spondylolisthesis Traumatic fractures • Congenital disease • Severe kyphosis • Severe scoliosis • Transitional vertebrae Spondylolysis Discogenic pain Segmental instability	Neoplasia • Multiple myeloma • Metastatic carcinoma • Lymphoma and leukaemia • Spinal cord tumours • Retroperitoneal tumours • Primary vertebral tumours Infection • Osteomyelitis • Septic discitis • Paraspinous abscess • Epidural abscess • Shingles Inflammatory arthritis • Ankylosing spondylitis • Psoriatic spondylitis • Reiter syndrome • Inflammatory bowel disease Scheuermann's disease Paget's disease	Pelvic organ involvement • Prostatitis • Endometriosis • Pelvic inflammatory disease Renal involvement • Nephrolithiasis • Pyelonephritis • Perinephric abscess Aortic aneurysm Gastrointestinal involvement • Pancreatitis • Cholecystitis • Penetrating ulcer

However, in a population setting, there is a significant association of higher disc degeneration grades on MRI in individuals with back pain compared to those without low back pain of the same age [35]. Disc degeneration seems to be related to an initial structural defect involving the endplate in young individuals or the annulus in older individuals [20,21,23,36–43]. Degenerative changes in the disc can be caused by mechanical [9,12], inflammatory [21,24–28,44], genetic [7,8,11,21,42,45–48], and infectious [31–33,49–51] factors. However, an exact cause of the pain and the degenerative changes cannot be identified in most instances [7,52,53]. Disc degeneration causes a loss of pressure in the nucleus and high stress-strain concentrations arise in the posterior part of the disc's annulus, which impaires nucleus cell matrix synthesis and change the biochemistry of the disc [37,42,54]. Moreover, inflammatory mechanisms are involved and further add to the catabolic process [55] with the loss of hydrophilic glycosaminoglycans (GAGs) [54]. These changes results in reduced water content within the nucleus pulposus, and the discs appear as "black discs" or "dehydrated discs" on water sensitive MRI sequences [56,57]. The reduced nucleus volume and pressure allows the annulus to bulge radially outwards like a 'flat tyre' [37]. As part of the degenerative process, radial fissures in the annulus progress outwards from the nucleus, usually posteriorly or posterolaterally. These degenerative changes in the annulus may eventually result in the disc prolapsing and be the cause of MRI findings such as annulus tears, Hyper Intensive Zones (HIZs), protrusion, extrusions, bulging and/or sequestration [37,41,58].

Clinical assessment

A proper diagnosis is essential, as this is the basis for the treatment and further handling of the low back pain patient. Therefore, the clinical assessment serves as a vital part of ruling out differential diagnoses, especially to identify "red flag" symptoms, e.g. suspicion of cancer or fractures, fever, bladder or bowel incontinence, loss of anal sphincter tone, saddle anesthesia, major motor deficit of the lower extremities, neurologic findings persisting beyond one month) and/or biopsychosocial factors. Cases with radicular pain and neurological symptoms are often easily recognised, and most physicians would advocate additional diagnostic imaging [18]. However, low back pain with referred pain from structures in the lumbar region can be a more complicated matter [9], and it is a well-known fact that lumbar spine imaging has a poor correlation with the clinical presentation in these patients [12,19,59]. This issue can be frustrating for both physicians and patients, and has led to increasing interest in new imaging techniques of the lumbar spine – e.g. weight-bearing MRI.

CONVENTIONAL MAGNETIC RESONANCE IMAGING

MRI

Although the causes of low back pain are difficult to detect, degenerative structural changes of the spine do account for the symptoms in some cases, and therefore MRI of the lumbar spine has, today, an established role in the diagnostic assessment. The Organization for Economic Co-operation and Development (OECD) has reported an increase in both the number of installed MRI scanners, and the absolute number of MRI examinations has more than doubled between 2000 and 2013 [60].

The conventional MRI system magnetic field strength typically ranges from 1.0 to 3.0 Tesla and is often referred to as "high-field MRI", or superconducting helium cooled MRI scanners [61,62]. In comparison, the strength of the Earth's magnetic field is 5×10^{-5} Tesla. The high static magnetic field inside the scanner causes some of the hydrogen atom nuclei (protons) in water and lipid molecules to snap into alignment with the magnetic field. The alignment can be either parallel (low-energy state) or antiparallel (high-energy state) to the magnetic field. A radio frequency coil produces an electromagnetic pulse causing the aligned protons to transition into the high-energy state. As the radio frequency coil stops its pulse, the protons in the patient then return to the low-energy state and a signal is induced in the scanner's receiver coil. The MRI signal is then transformed into images by the Fourier transformation algorithm [63].

Magnetic resonance imaging protocols

The usual MRI protocols of the lumbar spine includes sagittal T1-weighted (T1w) Turbo Spin Echo (TSE), sagittal and axial T2-

weighted (T2w) TSE images. Further, T2w images of the coronal plane are recommended [64,65]. In T1w images without spectral fat saturation, areas of high signal intensity indicate high-fat concentration, whereas in T2w images without fat saturation, high signal intensity is seen in both fluid-containing tissue and fatty tissue. Thus, T2w images are suited to assess disc degeneration due to loss of water caused by the degenerative changes in the disc matrix [66].

The fatty tissue may obscure MRI findings on the T2w images without fat saturation [67]. To overcome this issue, spectral fat suppression T2w or fluid sensitive sequences with fat saturation such as the Short Tau Inversion Recovery (STIR) sequences have been developed [67]. STIR is a robust fat-suppression technique sensitive for detection of oedema in i.e. neoplastic, infectious, and traumatic pathologies. However, STIR is less useful for assessment of degenerative changes due to a higher degree of noise and lower resolution compared to spectral fat saturated T2w images [68].

Positioning of the patient during MRI

To increase the patient's comfort and ensure motionless imaging, the patients are often scanned in the supine position with a pillow under the lower legs [69–71]. This position results in slight flexion of the hip, which in turn reduces lumbar tension and the risk of movement artefacts. However, studies have indicated that this position may cause underestimation of some degenerative conditions such as spinal stenosis, and it is suggested that patients should preferably be imaged with straightened lower extremities in the supine position [69,71].

MRI findings

Attention has previously been on "abnormal" morphological findings of the lumbar structures, which have been assumed to cause the back pain [9,72]. Moreover, instability of one or more spinal segments is believed to be a pain generating MRI finding, and the increasing number of fusion operations on the spine adds support to this belief [9]. However, evidence has lately pointed to a more multifactorial aetiology. As previously discussed, changes in tissue found on MRI such as disc degeneration and Modic changes have been found to be associated with low back pain [22,32,35,40,44,71]. Therefore, degenerative MRI findings may be divided into: *tissue property changes* (e.g. discus degeneration, Modic changes and facet arthropathy) or *pathoanatomical findings* (e.g. herniation, herniation grad, foraminal stenosis, spinal stenosis, spondylolisthesis, HIZ, facet joint effusion and segmental instability) [72]. (**Table 4-6)**

Pathoanatomical findings and changes in the tissues are common in individuals, both with and without low back pain [19,23,35,73–75] and the findings often correlate poorly with the clinical presentation on an individual level [7,13,18,19,73,75–77]. For this reason, many physicians often distinguish between "age-related" and "pain-related" degenerative MRI findings in the lumbar spine; although there is no precise definition to differentiate between the two [37,41,53]. Despite these limitations, patients seem to expect some kind of imaging procedure and expect the cause of their pain to be identified by it [78]. These expectations may have added to the interest in new imaging techniques of the lumbar spine, such as weight-bearing MRI.

WEIGHT-BEARING MRI

The typical weight-bearing MRI system has a field strength (< 1 Tesla), where the magnet design allow images to be obtained in sitting or standing positions – known as positional MRI (pMRI) [61]. Three different scanners can be seen in **Figure 1A-C.**

Table 2
Variations of weight-bearing MRI modalities based on Jinkins et al. [79]

Supine/recumbent MRI	rMRI	Recumbent refers to the unloaded position with the patient lying down. However, most studies use the term supine MRI as the patient is typically scanned on their back with a pillow supporting the lower extremities.
Positional MRI	pMRI	Imaging in varying weight-bearing positions (e.g. standing, seated or in the position which worsens symptoms).
Kinetic MRI	kMRI	Static imaging of kinetic manoeuvres (e.g., flexion, extension, rotation, lateral bending)
Dynamic MRI	dMRI	MRI while the spine is moving. Serial images show the dynamic movement of morphology.

Some configurations allows images to be obtained during flexion-extension, left-to-right rotation or left-to-right bending manoeuvres - known as kinetic MRI (kMRI) [79,80]. See **Table 2** for more definitions**.** Flexion-extension kMRI was designed to simulate the lumbar myelography, and a good correlation between the modalities has been found [81]. Therefore, kMRI seems to be a feasible alternative to the myelography, which also suffers from the risk of infection, adverse contrast agent reactions, and spinal headache. During flexion-extension kMRI the patient bends over a bar to reduce body motion and maintain positioning [71,79,82]. Therefore, standing pMRI should, in theory, more closely approximate the in vivo situation where the lumbar spine is affected by the tone in the paraspinal and abdominal musculature [70,79,83].

Figure 1A (left): Paramed Medical Systems MrOpen™, a 0.5 Tesla cryogen-free superconductive MRI system allowing imaging of the lumbar spine in the supine, standing and seated positions. In addition, the system allows flexion-extension kMRI and pMRI of weight-bearing extremities. FDA approved the system in 2008. (www.paramed.it) Reprint with permission. **Figure 1B (middle):** Fonar Upright® Multi-Position™ is a 0.6 Tesla MRI system allowing imaging of the lumbar spine in the supine, standing and seated positions. In addition, the system allows flexion-extension kMRI and pMRI of weight-bearing extremities. FDA approved the system in 2000. (www.fonar.com) Reprint with permission. **Figure 1C (right)**: ESAOTE G-scan is a 0.25 Tesla MRI system allowing imaging of the lumbar spine in the supine and standing positions. In addition, the system allows pMRI of the weight-bearing extremities. FDA approved the system in 2004. (www.esaote.com) Reprint with permission.

PHYSIOLOGICAL CHANGES IN WEIGHT-BEARING MRI

As previously mentioned, patients are typically scanned in the supine position with a pillow under the lower legs, which results in flexion of the hip and the lumbar spine [69–71]. Several studies have reported that the lumbar lordosis angle increases in the standing scanning position compared to the conventional supine position [70,84] or the neutral seated position [82]. (**Figure 2**.) Adding load in a backpack during the standing scan seems to

increase the lumbar lordosis angle even more [85,86]. Despite this, it has been reported that the supine position with stretched legs may result in a similar lumbar lordosis angle as that found in the standing position [71,82]. Several studies have investigated changes in the lumbar spine's dimensions during standing pMRI compared to conventional supine MRI, and have reported that the spinal canal, dural sac and neuroforaminal size decreases in individuals both with and without low back pain [70,79,81,82,87–90]. These changes may partly be explained by an increased thickness in the ligamenta flava [87], and an increased posterior disc curvature [87,91–94], which are both found in the upright position and/or with extension of the lumbar spine. These dimensional changes may, to some extent, represent the physiological changes in response to changing from the supine to the upright position. An overview of physiological changes is given in **Figure 3**.

POSITIONAL DEGENERATIVE CHANGES IN WEIGHT-BEARING MRI

Several studies have reported dynamic changes in degenerative pathoanatomical findings during MRI in the upright position. In the following, an overview of the literature will be given with complementary cases from our clinical cohort.

Herniation

Herniations (i.e., disc bulging, protrusions and extrusions) are common degenerative findings. Disc bulging seems to be very sensitive to changes in the lumbar lordosis and disc bulging has been diagnosed in 12-27% more discs during extension compared to flexion in the upright position in the same low back pain patient [97,98]. Moreover, the size of disc herniations has been found to increase with extension [89,92,93]. It has also been reported that posterior disc herniation can increase in size with flexion in discs with severe degeneration [89]. This paradox is believed to be a caused by degenerative weakness of the posterior longitudinal ligament [80]. Standing pMRI also seems feasible to detect hidden disc herniation or nerve root compression [83,84]. See **Figure 4A and 4B**

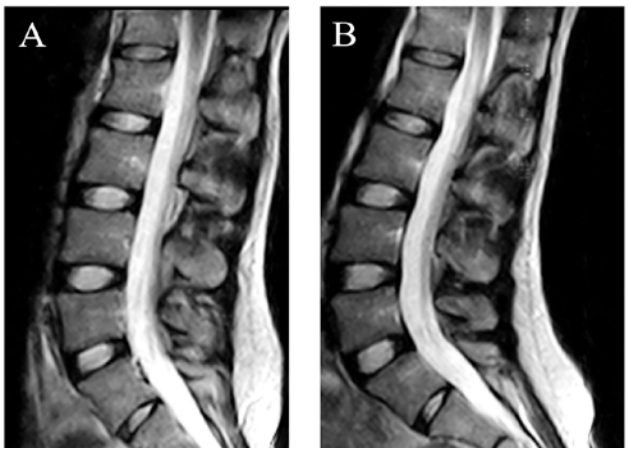

Figure 2, T2 mid-sagittal images of the lumbar spine in a young female patient. (A) In the conventional supine position with a pillow under the legs and (B) In the standing weight-bearing position. Note the increased lordosis angle in the standing position.

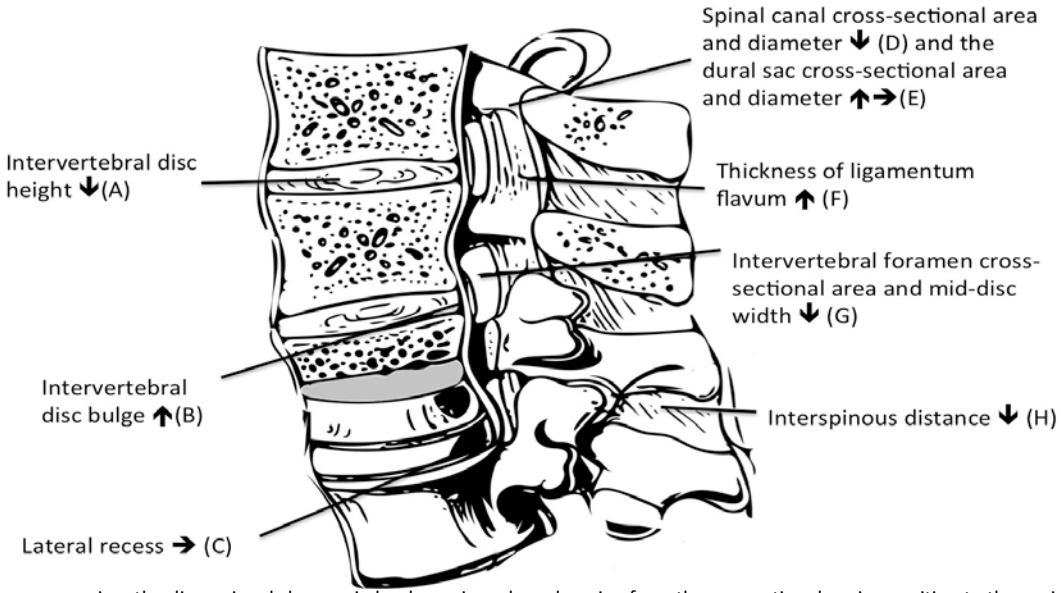

Figure 3, The figure summarises the dimensional changes in lumbar spine when changing from the conventional supine position to the upright position. (A) The overall disc height decreases [84,85,91,95]. However, some studies report changes in the discs' configuration i.e. the anterior disc height increases and the posterior disc height decreases [80,91,95], and this characteristic seems to decrease with increasing degeneration of the discs [95]. (B) The intervertebral disc bulge or posterior contour increases in size [87,91–93], which seems to increase in size with the severity of disc degeneration [92]. (C) Lateral recess (i.e., subarticular zone) decreases in size in the upright position in healthy individuals [87] and in low back pain patients [79,81,90]. (D) The spinal canal cross-sectional area and diameter decrease in the upright position and further with extension of the lumbar spine [70,71,81,82,87]. (E) The dural sac cross-sectional area and diameter decreases in size in the upright position and with lumbar extension [70,79,81,88,89]. However, in healthy individuals, an expansion of the dural sac has been observed in the lower lumbar spine due to the lumbar fluid (CSF) pressures increased in response to postural changes in the upright position [82]. (F) The thickness of ligamentum flavum increases in the upright position and further with extension of the lumbar spine [79,87,89,96,97]. (G) The intervertebral foramen cross-sectional area (neuroforarmen) decreases in size by an approximation of the pedicles, increased disc bulging, and increased thickness of the ligamentum flavum [70,80,87,89]. (I) The interspinous distance decreases as the lumbar lordosis angle increases in the upright position [84].

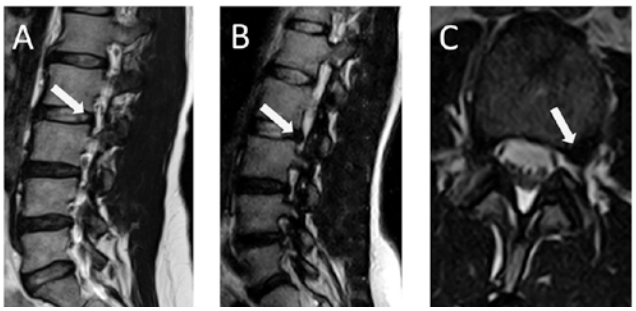

Figure 4A. A young male patient with radiating pain to the anterior femoral area predominating in the standing position. (A) Conventional 3Tesla T2w sagittal image of the patient's lumbar spine. (B) The same T2w sagittal image and (C) the L2/L3 axial T2w image of the patient in the standing position in the 0.25Tesla open MRI scanner (G-Scan). Note the mobile forarminal left-sided protrusion/bulging only visible in the weight-bearing position (arrows).

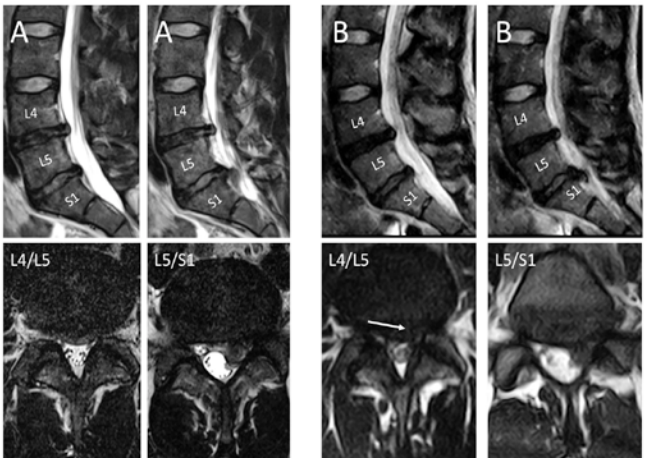

Figure 4B. A male patient with low back pain is scanned (A) in the conventional supine position in a 3Tesla MRI scanner and (B) in the standing position in the 0.25Tesla open MRI scanner (G-Scan). T2w sagittal images (top) and T2w axial image (below). The L5/S1 extrusion does not seem to change configuration between positions; however, the L4/L5 protrusion seems to migrate laterally in the standing images and display left-sided nerve root compression (arrow).

Neuroforarminal stenosis and lateral recess stenosis

Neuroforaminal stenosis and lateral recess stenosis increases in number and severity in the standing position, due to a decreased disc height, increased bulging of the annulus fibrosus and increased thickness of the ligamentum flavum [89,99]. Low back pain patients imaged in the sitting position with an additional extension of the lumbar spine has resulted in a change of diagnosis to "neuroforaminal stenosis" in 22% compared to the conventional supine position [89]. Furthermore, several case reports have found that hidden lateral recess stenosis can only be visible during standing pMRI [79,100]. See **Figure 5.**

High Intensity Zones (HIZ)

HIZ represents an advanced annular tear and is believed to be a part of the degenerative spectrum in the disc. HIZ is visible on MRI as bright signal intensity in the posterior annulus that is brighter than the nucleus pulposus on T2-weighted images [101]. HIZ is believed to be associated with non-specific low back pain [101]. It has been suggested that the upright extended position may raise the intra-discal pressure, and this stress may force the fluid out of the semi-liquid nucleus into the posterior annular tear, resulting in an increased fluid signal in the posterior part of the disc [80,102]. When imaging in the standing position, the same phenomenon can be seen. See **Figure 6.**

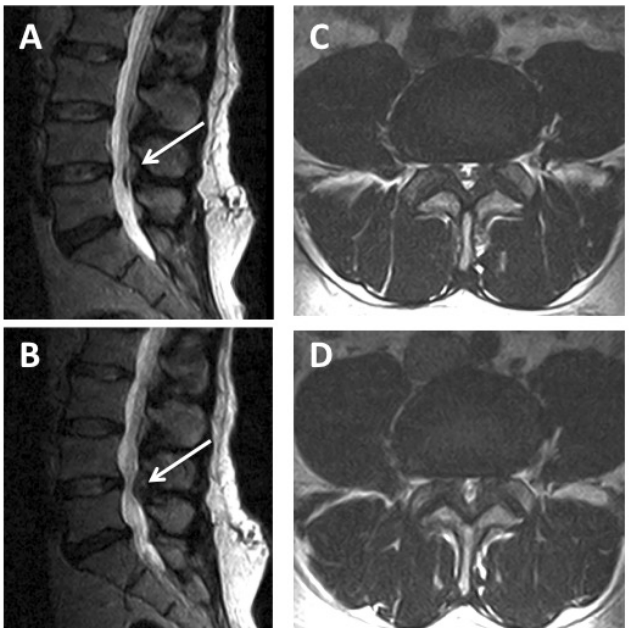

Figure 5. Six months after L5 hemilaminectomy and discectomy a patient experienced diffuse radiating symptoms to the right leg, especially in the standing position. Conventional supine MRI did not establish any clear diagnosis (A and C). Subsequently, standing MRI displayed lateral recess stenosis one level above the level of surgery, which correlated with the patient's symptoms (B + D). (Reprint of Hansen BB et al. [100] with permission from Ugeskrift for læger)

Spondylolisthesis

Spondylolisthesis is diagnosed when a displacement greater than 1 mm is present at an intervertebral disc level and is considered as anterolisthesis (forward slip) or retrolisthesis/retrodisplacement (backward slip) on the basis of the position of the upper (cephalic) vertebra [72]. Standing flexion-extension radiography is still widely used by spine surgeons to assess suspected instability in spondylolisthesis [76]. Flexion-extension kMRI, have shown similar capability but provides additional information about stenosis and nerve root compression [79,103,104]. Standing pMRI also seems sensitive for detection of hidden spondylolisthesis [83,84]. See **Figure 7.** However, some studies indicate that this may also be found when scanning the patients in the supine position with straightened lower extremities [69,71]. Therefore, the influence of gravity and the lumbar lordosis on spondylolisthesis is not entirely understood.

Spinal stenosis

The severity of spinal stenosis increases in the upright standing position [83,84] and with the extension of the lumbar spine in the upright sitting position [79,81,90,105]. See **Figure 8**. This is in accordance with the symptomatology, which includes radiculopathy, back pain and muscular fatigue predominating in the standing position or during walking [106,107]. These classic symptoms may partly be explained by an increased thickness of the ligamenta flava found in the upright and extended position as a result of the increased lordosis [87].

Juxtafacet cysts

Juxtafacet cysts (synovial cysts) can be seen as a hyperintens cavity adjacent to the facet joint on fluid sensitive sequences like T2 weighted images. These cysts have been found to increase in

size in the upright position and with the extension of the lumbar spine in kMRI [84,108,109]. The cysts may communicate with the facet joint, where the intra-articular fluid can be pressed into the anterior and posterior recess as the superior articular process is pressed into the underlying inferior process in the standing position and upon lumbar extension. See this illustrated in **Figure 9**. These cysts may encroach (intraspinal or paraspinal) the central spinal canal, the lateral recesses and the neuroforamens, and in some cases cause nerve root compression [109,110].

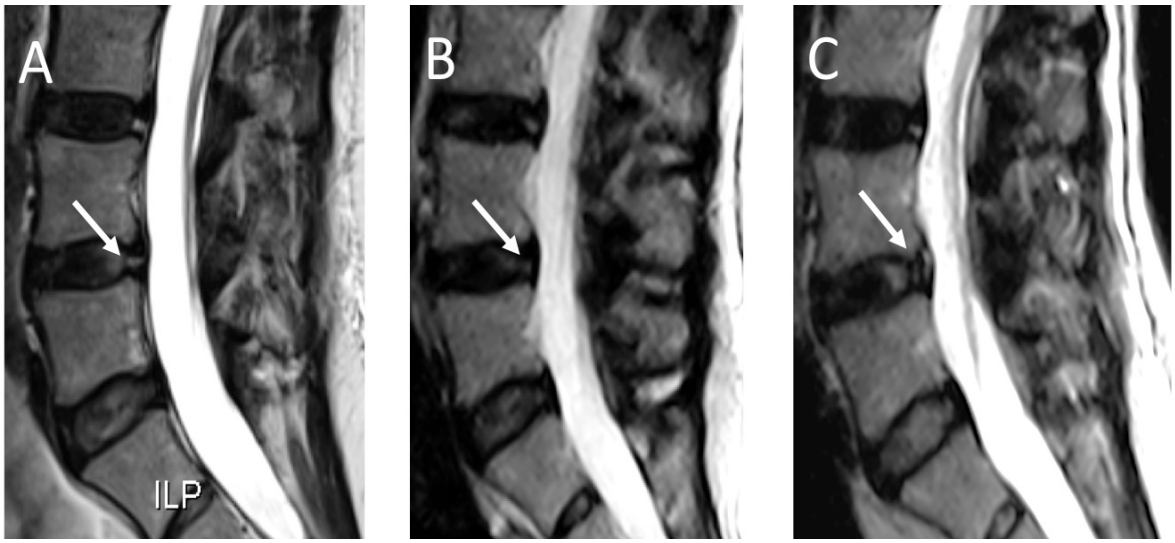

Figure 6. A patient with non-specific low back pain. (A) T2w sagittal images of the patient in the conventional supine position in a 3Tesla scanner. Note the annulus tear seen in the L4/L5 level. (B) The same image in the supine position in the 0.25Tesla open MRI scanner (G-Scan). Note that the full extend of the annulus tear is not visible due to the lower field strength. (C) The same image in the standing position in the 0.25Tesla open MRI scanner (G-Scan), the HIZ become visible in the cranial-posterior corner of the L4/L5 intervertebral disc.

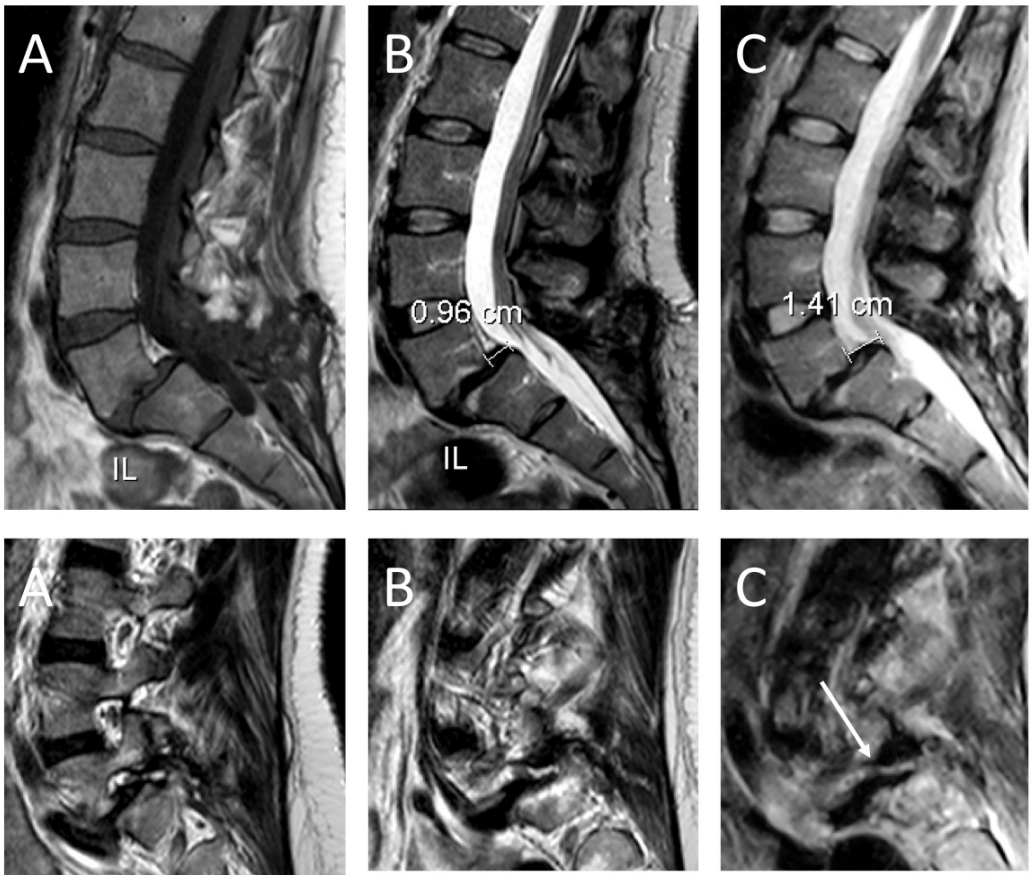

Figure 7. A young female with non-specific low back pain, retinopathy and increasing fatigue in her legs during standing. (A + B) T2w and T1w sagittal images of the lumbar spine in the conventional supine position in a 3Tesla scanner. (C) T2 weighted sagittal images in the standing position in 0.25Tesla open MRI scanner (G-Scan). Note the positional dependent instability at the L5/S1 segment and neuro-foraminal nerve root compression in the standing position (arrow).

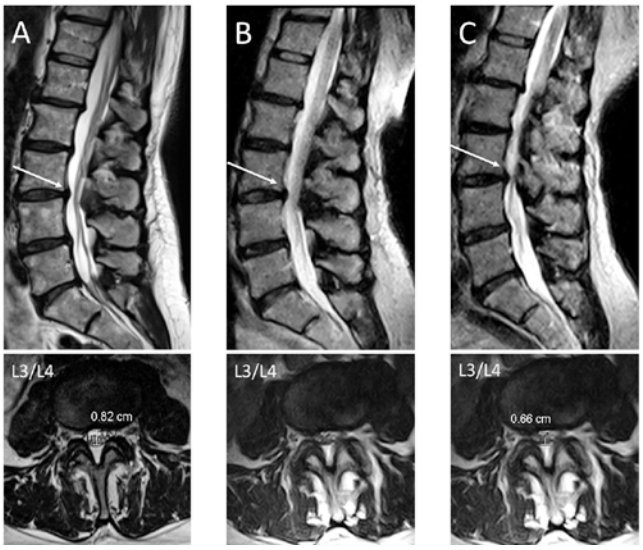

Figure 8. A male patient with non-specific low back pain, radiculopathy and muscular fatigue in the standing position and during walking. The patient was scanned (A) in the conventional supine position in a 3Tesla MRI scanner, (B) in the supine position in the 0.25Tesla open MRI scanner (G-Scan) and (C) in the standing position. T2w sagittal images (top) and T2w axial image (below). Note, the dural cross-sectional diameter and area decrease in the standing position revealing a more significant spinal stenosis.

Spinous process collision (Morbus Baastrup)

Spinous process collision (also referred to as kissing spines) results from adjacent spinous processes rubbing against each other. This collision tends to be more common in the elderly patients but can also be found in individuals with hypermobility syndrome. The patients often describe midline pain and tenderness relieved by flexion and aggravated by extension. The process can result in a degenerative hypertrophy, inflammatory change and even a pseudoarthrosis with bursa formation. See such a bursa formation in Figure 10. Further remodelling may lead to progressive interspinous degeneration and eventually anterior displacement of the interspinous ligament, and to some degree add to a stenosis of the central spinal canal [110].

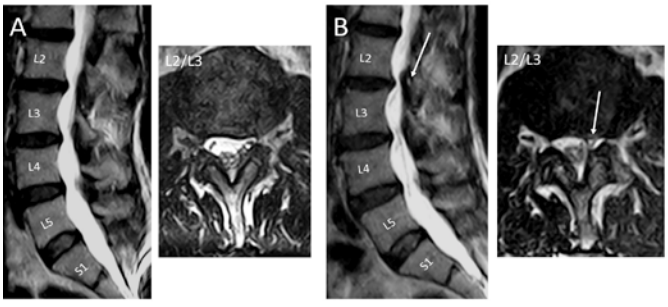

Figure 9. A male patient with radiating pain to the left-sided anterior femoral area when standing. (A) T2w sagittal and L2/L3 axial T2w images of the patient's lumbar spine in the conventional supine position in the 0.25Tesla open MRI scanner (G-Scan). (B) The same T2w sagittal image and L2/L3 axial T2w images with the patient in the standing position. Note the juxtafacet cysts (synovial cysts) and nerve root compression is only visible on the standing images (arrows).

Instability

Abnormal segmental motion/segmental instability (i.e. angulation and translation in the sagittal and coronal plane) are detectable with standing pMRI [83,84] or with flexion-extension kMRI [79,98,102,111]. Degenerative changes in the facet joints comprise cartilage degradation that leads to the formation of focal and then diffuse joint erosions, joint space narrowing, and sclerosis of the subchondral bone. This remodelling of the facet joints impairs the joint's function, which reduces axial rotation and forward sliding of the vertebrae[110]. Increased intra-articular fluid is related to the degenerative process of the facet joints. When a patient is scanned in the conventional supine position with a pillow under their legs, the intra-articular gap between the superior and inferior processes increases and the fluid becomes visible on fluid sensitive sequences i.e. T2w axial MR images [110]. This finding is often referred to as "facet joint effusion" when the fluid signal is greater than 1 mm [112].

Several studies have found a correlation between facet joint effusion on MRI and unstable slipping/angular movement on functional radiography or kMRI [113–115]. In upright kMRI, patients with advanced disc degeneration and facet joint osteoarthritis are found to be more stable in their lumbar spine compared to patients with moderate degenerative grades [111]. These results have indirectly supported Kirkaldy-Willis' three-phase disc degeneration theory (i.e. 1. dysfunction, 2. instability, and 3. restabilisation) [70,80,108,111,113,116]. Although, there is no clear definition for the term instability it is widely used and believed to be associated with low back pain [9]. Standing pMRI may in this perspective be an important additional examination for patients suspected of instability by facet joint effusion and moderate disc degeneration on their conventional supine MRI. See **Figure 11**.

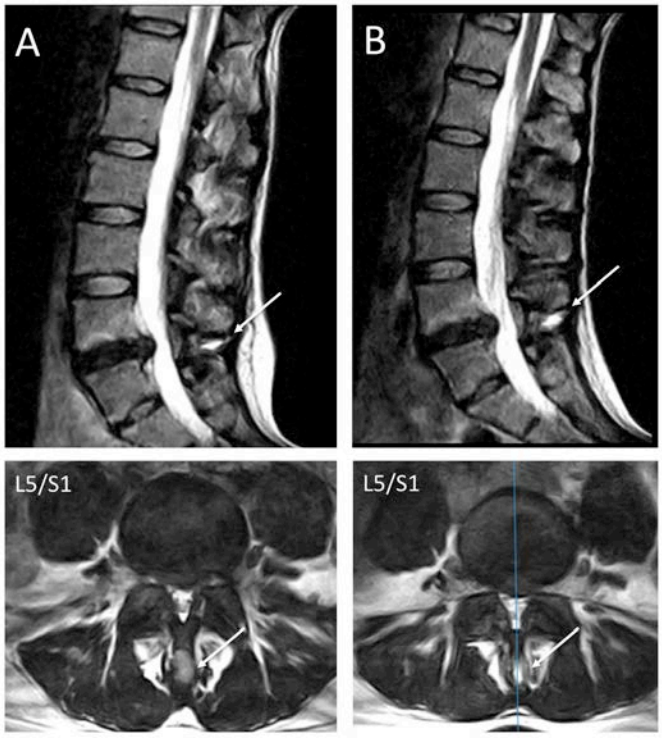

Figure 10. Female patient with non-specific low back pain. (A) T2w sagittal and L5/S1 axial T2w images of the patient's lumbar spine in the supine position in the 0.25Tesla open MRI scanner (G-Scan). (B) The same T2w sagittal image and L2/L3 axial T2w images with the patient in the standing position. The arrow in images B highlights a bursitis impingement; additionally, note that the hyperintensive bursitis becomes more diffuse in the standing position as a sign of compression (arrows).

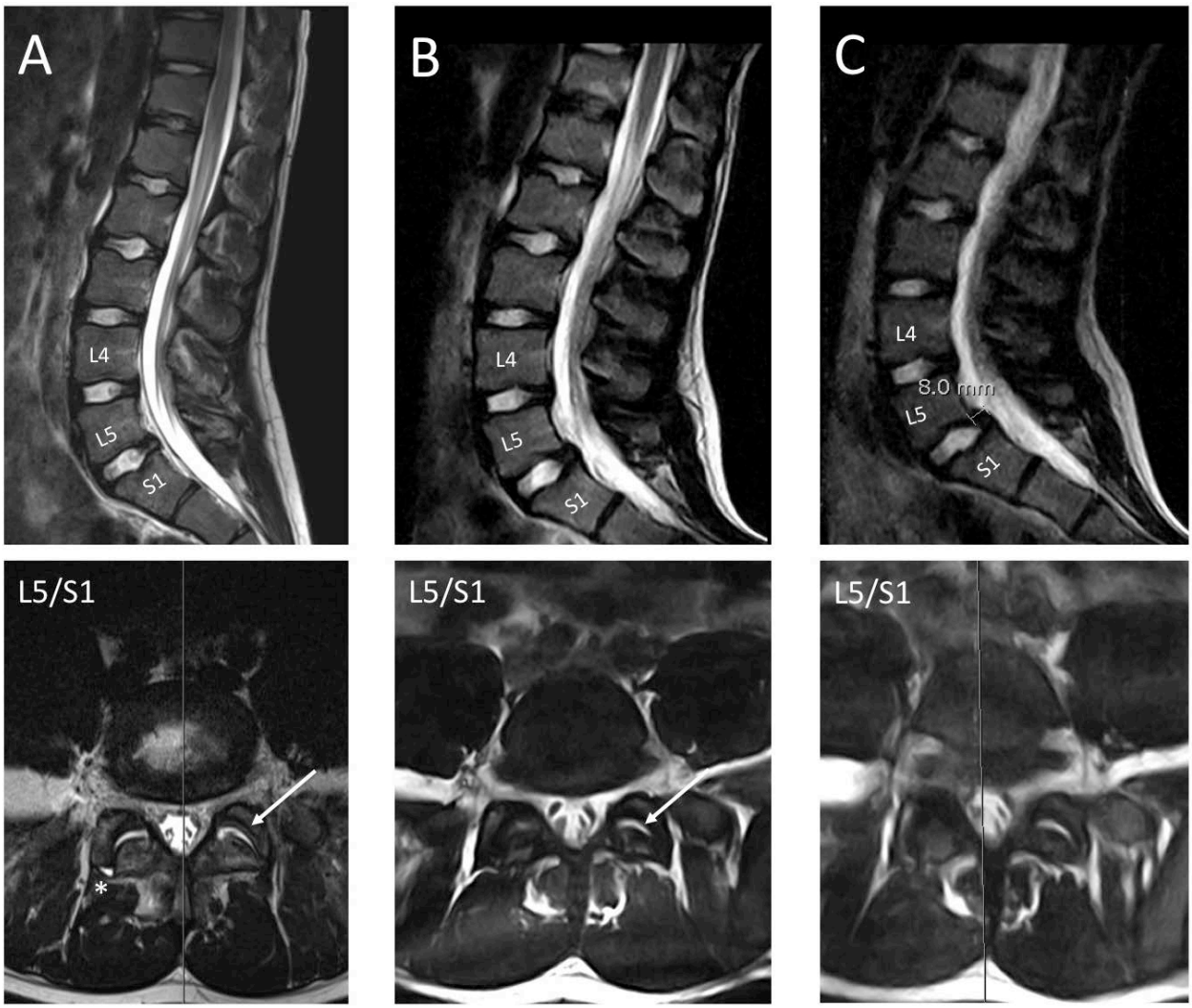

Figure 11. A young active athlete with low back pain, especially in the standing position. The patient was scanned (A) in the conventional supine position in a 1.5Tesla MRI scanner, (B) in the supine position in the 0.25Tesla open MRI scanner (G-Scan) and (C) in the standing position. T2w sagittal images (top) and T2w axial images (below). Note moderate disc degeneration, facet joint effusion and expansion of the posterior recess (*) on the axial images in both supine scans, indicating instability, which was only visible in the standing position (8 mm antrolisthesis).

THE THESIS' AIM AND OBJECTIVES

Before a full implementation of a novel diagnostic method, it is important to explore the diversity of the method's findings and potential adverse events and identify the most promising areas of interest before a decision is made to perform larger studies testing the precision of the diagnostic method. Thus the aim of the PhD thesis was to describe the introduction of standing pMRI (0.25 T G-Scan, ESAOTE, Italy) in the diagnostics of low back pain.

Study 1. Adverse events

A substantial risk of fainting (orthostatic syncope) was observed during standing pMRI. We aimed to study if an external pneumatic compression device, developed for the treatment of Deep Vein Thrombosis (DVT) could reduce the risk of fainting in standing pMRI [117].

Study 2. Disc degeneration, back pain and lumbar lordosis

The lumbar lordosis in the standing position is a significant contributor to positional changes in the lumbar spine. Disc degeneration and back pain are common in the typical patient referred to standing pMRI; therefore, we aimed to study if disc degeneration and back pain would affect pMRI outcomes by decreasing changes in the lumbar lordosis angle from the supine to the standing position [118].

Study 3. Reproducibility of positional changes in pMRI

Before applying standing pMRI in clinical use, it is important to know the reproducibility of common pMRI findings. Therefore, we aimed to study the interreader and intrareader reliability, and absolute agreement between three radiologists [119].

ETHICAL CONSIDERATIONS

The studies were designed to be observational, and therefore patients who entered the study received "usual care" by their treating physician during the studies. Due to the additional examinations as part of the studies, the patients were informed about the possibility of discovering additional abnormal findings. Therefore, before inclusion all participants were asked to decide if they wished to be informed about these findings. All included patients gave informed consent and the studies were approved by the local ethics committee (KF 01-045/03 and H-2-2013-155) and the Danish Data Protection Agency (01758 FRH-2012-003).

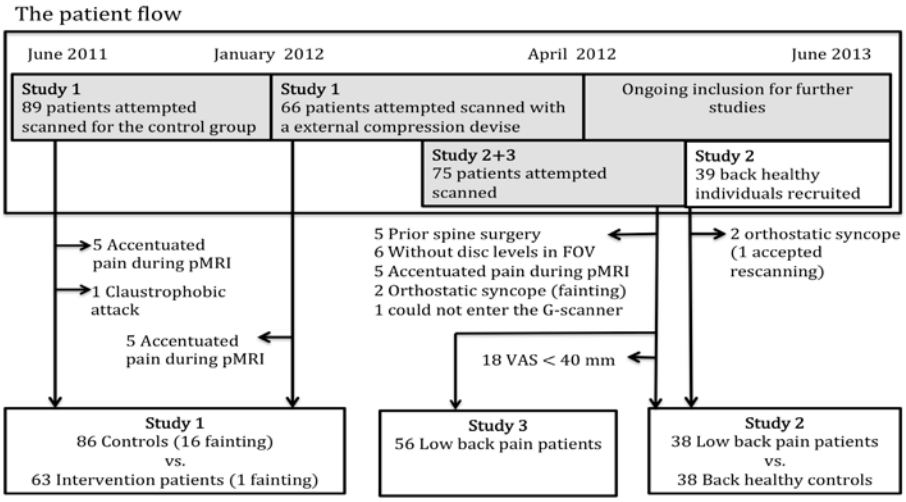

Figure 12. Flow chart describing the inclusion, patient screening process and the matching control group. FOV, field of view; LBP, low back pain; VAS, Visual Analogue Scale.

METHODS

Design

The first two studies in this thesis were observational in design and performed to explore the harms, benefits and potential confounders of a novel imaging technology [61]. The designed and reported outcomes were in accordance with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) [120]. The 3rd study was designed and reported in accordance with the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) [121].

Table 3.
Details of the magnetic resonance imaging sequences

	Standing weight-bearing (82^0)		Supine (0^0)		
	Sagittal TSE-T2	Axial 3DHYCE GE-T2	Sagittal TSE-T2	Axial 3DHYCE GE-T2	Sagittal TSE-T1
TR, msec	4370	10	4370	10	590
TE, msec	120	5	120	5	20
ST, mm	4		4		5
SBS, mm	0.5		0.5		0.5
FOV, mm	224*200	210*210	224*200	210*210	224*200
Acquisition_Matrix	224*200	180*180	224*200	180*180	256*168
Interpolated_matrix	512*512	512*512	512*512	512*512	256*256
Time, minutes	5.28	5.21	5.28	5.5	4.44

TSE-T2 = T2-weighted turbo spin-echo; 3DHYCE GE-T2 = T2 weighted 3D hybrid contrast enhancement gradient echo; TSE-T1 = T1-weighted turbo spin-echo; TA = acquisition time; TR = repetition time; TE = echo time; ST = slice thickness; SBS = spacing between slices

Participants

From June 2011 to June 2013, patients were recruited from the outpatient clinic of the Department of Rheumatology, Frederiksberg Hospital, Denmark and private spine surgery/rheumatology clinics in the Copenhagen area. Patients with low back pain over 18 years of age, with or without sciatica referred to a conventional MRI of the lumbar spine, were consecutively enrolled. Exclusion criteria were clinical scoliosis and "red flag" symptoms. In study 2 and 3, patients with previous spine surgery were excluded. See the full enrolment in Figure 12.

Imaging Acquisition

In all studies the participants first completed the standing pMRI followed by the supine MRI in a 0.25 T open MRI scanner (G-Scan, ESAOTE, Italy). The standing scans were performed with the participant leaning 82° posteriorly toward the scanner's inclined table to minimise motion artefacts. The standing sequences included a sagittal Turbo Spin Echo (TSE) T2w and an axial Gradient Echo (GRE) T2w sequence. (Table 3). During the supine scan, all participants were positioned in a psoas relaxed position with a pillow under the knees that was elevated approximately 15 cm from the horizontal table [70,71]. The patient positioning is shown in Figure 13. The supine scanning included sagittal turbo spin echo (TSE) T2w and T1w sequences equal to a standard conventional supine MRI and an axial 3D gradient echo (GRE) T2w sequence called 3DHYCE®.

DEGENERATIVE MRI EVALUATION

The degenerative MRI findings followed international nomenclature and validated semi-quantitative grading system. The outcomes were divided into:

1. *Degenerative pathological changes* (i.e. herniation, spinal stenosis, spondylolisthesis, High Intensive Zone (HIZ), facet joint effusion and juxtafacet cysts) Described in details in **Table 4.**
2. *Semi-quantitative degenerative pathological grading.* Described in details in **Table 5.**
3. *Degenerative tissue properties* (i.e. disc degeneration, Modic changes, facet arthropathy). Described in details in **Table 6.**

The degenerative findings were evaluated in consensus by a minimum of two radiologists in study 2, as this method have proven to be robust and reliable [122]. Due to the design of study 3, the degenerative findings and the semi-quantitative MRI grading were evaluated independently in order to test reliability and agreement.

Figure 13 The positioning of the participants in the standing position (left) and supine position (right).

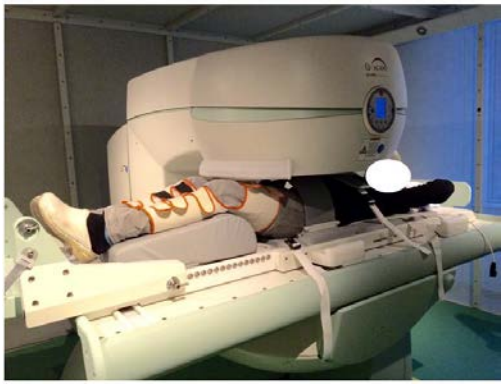

Table 4.
Degenerative pathological outcomes

Outcome	Author [ref]	Description
Herniation	Fardon et al.[123]	Disc herniation was defined as localised displaced disc material beyond the limits of the intervertebral disc space and divided into: • Protrusion was defined as a herniation less than 180° of the disc's circumference • Extrusion was defined as a herniation greater than the distance between the edges of the base in the same plane • Bulging was defined as a herniated disc greater than 180° of the disc's circumference • Schmorl's node was defined as an intervertebral herniation breaching the endplate in at least one scan plane.
Spinal stenosis	Binder et al.[106]	Lumbar spinal stenosis was defined as a combination of a dural cross-sectional diameter less than 10 mm and lateral recesses less than 2mm.
Spondyl-olisthesis	Carrino et al.[72]	Spondylolisthesis was defined as present when a displacement of greater than 1 mm was identified at the intervertebral disc level. On the basis of the position of the upper vertebra, the spondylolisthesis was classified as: • Anterolisthesis (forward slip) • Retrolisthesis (backwards slip)
Hyper intensive zone (HIZ)	Aprill et al.[101]	HIZ was defined as an area of bright signal intensity in the posterior annulus that was brighter than the nucleus pulposus on T2w images.
Facet joint effusion	Schinnerer et al.[112]	Facet joint effusion was defined as a curvilinear high-intensity signal greater than 1 mm between the articular processes on the axial T2w images.
Juxtafacet cysts	Spinner et al. [109]	Juxtafacet was defined as a high-intensity signal fluid-filled sac that is found in the anterior part of the facet joint and related to the synovium of the zygapophyseal facet joints.

Table 5.
Semi-quantitative grading of the degenerative lumbar pathological outcomes

Outcome	Author [ref]	Description
Herniation, nerve root compression	Pfirrmann et al. [124]	Herniation was graded according to nerve root compression. • Grade 0 (normal): No compromise and preserved epidural fat layer between the nerve root and the disc mat. • Grade 1 (contact): Normal position of the nerve root and visible contact of disc material with the nerve root. • Grade 2 (deviation): The nerve root was displaced dorsally by disc material. • Grade 3 (compression): The nerve root was compressed between disc material and the wall of the spinal canal.
Foraminal stenosis	Lee et al. [99]	Foraminal stenosis was graded on the sagittal MR images and included disc contour, degree of epidural fat obliteration and the compression of the nerve in the neuroforamina: • Grade 0: (normal) absence of foraminal stenosis. • Grade 1: (mild) perineural fat obliteration in one of the two opposing directions (vertical or transverse). • Grade 2: (moderate) perineural fat obliteration in all four directions (both vertical and transverse), but without morphologic changes. • Grade 3: (severe) nerve root collapse and/or morphologic change on the nerve root.
Lumbar spinal stenosis	Guen et al. [125]	Central spinal stenosis was graded by separation of the cauda equina and obliteration of the cerebrospinal fluid (CSF) space in front of the cauda equina in the dural sac on T2w axial images: • Grade 0: (normal) the anterior CSF space is not obliterated. • Grade 1: (mild) the anterior CSF space is mildly obliterated, but all cauda equina can be clearly separated from each other. • Grade 2: (moderate) the anterior CSF space is moderately obliterated, and some of the cauda equina are aggregated, making it impossible to separate them visually. • Grade 3: (severe) the anterior CSF space is severely obliterated, and none of the cauda equina can be visually separated from each other (appearing instead as one bundle).

Table 6.
Semi-quantitative assessments of tissue properties

Outcome	Author [ref]	Description
Discus degeneration	Pfirrmann et al. [56]	Disc degeneration was graded according to the following: • Grade I: a homogeneous nucleus pulposus, high T2w-signal intensity, clear distinction of the nucleus/annulus, and normal disc height. • Grade II: a light inhomogeneous nucleus pulposus, clear distinction of the nucleus/annulus and with or without horizontal grey bands. • Grade III: an inhomogeneous nucleus pulposus, unclear distinction of the nucleus/annulus and slightly decreased disc height. • Grade IV: an inhomogeneous nucleus pulposus, no distinction of the nucleus/annulus, low signal intensity, nucleus and the annulus is lost/moderately degenerated. • Grade V: an inhomogeneous and hypointense nucleus pulposus, no distinction of the nucleus/annulus and a collapsed disc space.
Modic changes	Modic et al. [20]	Endplate marrow changes were classified according to the following: • Type 1: low T1w and a high T2w signal of the subchondral bone marrow (increased vascularisation). • Type 2: high signal in both the T1w and T2w signal (fat-like signal). • Type 3: low T1w and T2w signals (sclerosis-like signal).
Facet joint osteoarthritis	Weishaupt et al. [88]	Facet joint osteoarthritis was graded on the axial T2w and T1w MR images. • Grade 0 (Normal): facet joint space between 2-4 mm. • Grade 1 (Mild): facet joint space (< 2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process. • Grade 2 (Moderate): narrowing of the facet joint space and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions. • Grade 3 (Severe): 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.

STUDY 1: BACKGROUND

At the start of 2011, we began including patients with low back pain for standing pMRI and immediately experienced that some of the patients fainted during the standing scan. Since the technology was novel, this issue was unrecognised and not reported in the literature. With an average of one fainting episode a day, we realised that we could not continue our studies.

It was speculated that the prolonged standing decrease the return of blood from the lower extremities, thereby, causing a critically low filling of the left ventricle and eliciting the Bezold–Jarisch reflex causing syncope through vasodilatation and/or bradycardia [126–128], also known as the "fallen soldier phenomenon" [126–128]. Therefore, we hypothesised that a device designed to increase the return blood velocity in the deep veins could prevent the fainting. Such a device (Huntleigh Flowtron Excel DVT Pump, Bedfordshire, UK) was commercially available and used during surgery to prevent DVT by applying oscillating external pneumatic compression to the legs [129]. We contacted the manufacturer of the pump system and had two extension tubes made so the pump system could be placed outside the Faraday cage, without interfering with the imaging process (**Figure 14).** The aim of this study was to reduce the risk of fainting in standing pMRI by introducing a peristaltic external pneumatic compression device.

STUDY 1: METHODS

We decided to create a three-month intervention period using the external pneumatic compression device in the standing position and a retrospective group was used as controls. Fainting was defined as a partial/full collapse or near syncope (e.g., dizziness, severe light-headedness, and nausea) resulting in the patients' use of the scanner's emergency button, thus interrupting the standing MRI sequence. In case of fainting, the scanner's data was analysed and the time from the first scout sequence to the interrupted sequence was measured.

STUDY 1: RESULTS

We attempted to scan a total of 155 patients (83 female) but had to exclude six patients due to reasons other than fainting during standing pMRI. The full enrolment can found in **Figure 12.** The final patient sample was based on 149 patients (80 female) with no differences in age or gender between groups. We were able to reduce fainting during the standing examination from 19% to 2% with the pneumatic compression device. The difference between groups was statistically significant (p=0.0011) in favour of the experimental compression device (**Table 7**).

For the purpose of sensitivity, logistic regression tested adjustment for the two potential confounders (age and gender) simultaneously, and the result was still statistically significant (OR=0.072; p=0.012), without the influence of age (p=0.37) or gender (p=0.71). The patients who fainted were eight females and nine males with an average age of 39.6 ± 11.2 years and age range of 26–57 years. See **Figure 15** for further details. Except for the discomfort of fainting no adverse effects were seen following the episodes, and no patients experienced injuries or required medical attention after the episode.

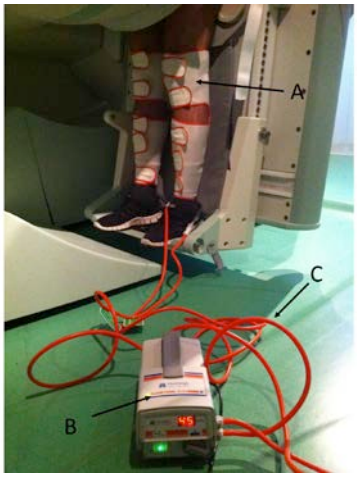

Figure 14. The figure show a patient in the standing position of the positional MR examination with a compression cuff around each leg (A) connected to the Huntleigh Flowtron Excel DVT Pump (B) by two custom-made extension tubes (C).

STUDY 1: DISCUSSION

Principal finding

The substantial risk of fainting during standing pMRI was almost eliminated by the use of an easily applied external pneumatic compression device around the legs to compensate for the reduced muscle pump in the standing position.

Strength and limitations of the study

Conventional MRI has the privilege of being associated with very few adverse effects or events; however, a new dynamic approach should still be thoroughly assessed for potential harm before introduction into clinical practice [61]. To our knowledge, this is the first study systematically collecting data on fainting and near fainting episodes during standing pMRI, and the first study to test an easily applied intervention against the issue. The study was conducted in a patient group with low back pain; however, we are confident that our results could be generalised to other standing examinations or situations can be an issue. More importantly, this study highlights a potential adverse event that all patients referred to standing pMRI should also be informed about this issue before initiating the scan [89,130].

A methodological limitation is that one part of the study was retrospective, and only the intervention group was included prospectively. Ideally, a real randomised trial should have been conducted where the patients were randomised to either intervention with the device or without. However, the relative risk (RR) of fainting without pneumatic compression device was 11.7 (Wald-test converted 95 % CI: 2.67 to 51.40), and therefore we found it unethical to do a second prospective study.

Perspectives and future research

It has been suggested that wearing compression hosiery during the standing examinations may also reduce the risk of fainting [70]. Compression hosiery may be an alternative in some patient groups, and therefore future studies should test compression hosiery against the pneumatic compression device.
Interruption or non-completion of the upright scan due to worsening of pain or neuropathy have been reported in both pMRI and kMRI [89,130]. This issue may also cause unwanted and unplanned motion during the standing scan, thereby reducing image quality due to movement artefacts [95]. Therefore, future studies should investigate this matter, and sequence and software development should try to include movement correction algorithms to compensate for this during the upright scan.

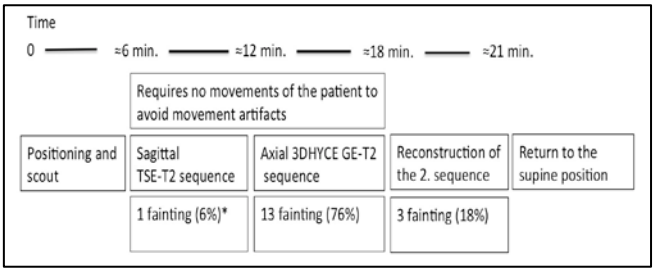

Figure 15. The sequences and fainting during the standing scan. * A 27-year-old highly trained athlete fainted just 3 min. after the beginning of the first sequence.

Table 7.
Study characteristics and statistical tests comparing groups study 1

	Device (N=63)	No device (N=86)	Difference between groups (95% Confidence Interval)		P-value
Females, no (%)	36 (57%)	44 (51%)	OR=1.27	(0.66 to 2.45)	0.47
Age, years	43.3 (13.4)	41.9 (11.8)	MD=1.4	(-2.8 to 5.6)	0.51
Fainted, no (%)*	1 (2%)	16 (19%)	*OR=0.071	*(0.002 to 0.49)	*0.0011

Binary data: Analysed using Chi-square tests from the 2x2 contingency table; the Odds Ratio applied for the comparison between the groups. Continuous data (age): presented as the difference between means; analysed using two-sample t-test assuming an unequal variance by default. *Based on Fisher's exact test (two-sided), with the corresponding (exact) Odds Ratio (95% CI).

STUDY 2: BACKGROUND

It is believed that positional changes in the lumbar spine morphology during standing pMRI is a consequence of multiple factors such as gravity, the action of the core muscles and especially increased lordosis [70,79,80,84]. Illustrated in **Figure 16.**
Extension of the lumbar spine leads to increased lordosis, and this is assumed by many to be a main contributor to positional changes in weight-bearing MRI e.g. enlarged disc herniation, protrusion, ventral slippage, and spinal stenosis [71,81,87,88,92,93]. With increasing disc degeneration, the lumbar lordosis is assumed to ''flatten'' as the nucleus becomes smaller and decompressed [131,132], and patients with low back pain are believed to keep the spine straight to reduce pain [131,133]. Therefore, we hypothesised that the change in lumbar lordosis from supine to standing position would be negatively associated with both lumbar disc degeneration grade and low back pain score. Thus, the aim of study 2 was to test if disc degeneration and back pain would affect the lordosis angle change on pMRI outcomes towards a decreased lumbar lordosis angle potential from the supine to the standing position.

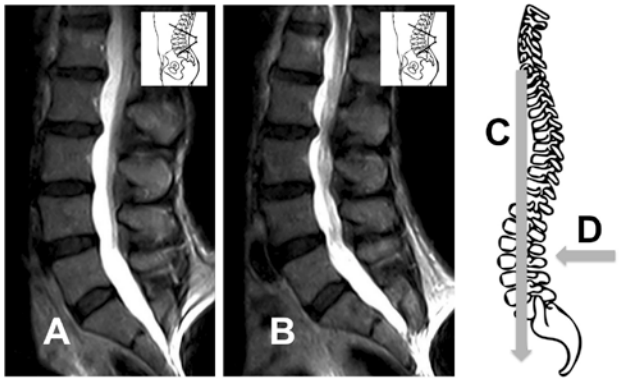

Figure 16. T2 mid-sagittal images of the lumbar spine in: (A) the conventional supine position, and (B) standing weight-bearing position. In standing pMRI, the lumbar spine is affected both by (C) gravity, (C) action of the para-spinal/abdominal musculature and, (D) increased lumbar lordosis.

STUDY 2: METHODS

The overall study group consisted of both low back pain patients and back-healthy individuals matching the patient group 1:1 in terms of number, sex, and decade of birth. Patients with light back pain and degenerative findings are very common and may

have extensive overlap with healthy individuals [19,23,35,73,75,118]. For this reason, the study only included patients with severe back pain defined as patients with a Visual Analog Scale (VAS) score above 40 mm during both activities and rest. The healthy individuals had no history of lumbar pain and defined themselves as ''back-healthy.'' Also, see the enrolment in Figure 12.

All participants had their supine MRI evaluated in consensus by of two radiologists for the degenerative disc findings described in details in Table 4-5. The radiologists were blinded to clinical information and group. A total lumbar degeneration disc score was calculated by summing all the L1 to L5 Pfirrmann's semi-quantitative disc grading [35,56]. The lumbar lordosis angle measurement was performed independently of the evaluation for degenerative MRI findings by a single observer. Due to the G-scanner's limited Field Of View (FOV) and potential geometric distortion in the boundaries of the images, the lumbar lordosis angle was defined as the angle between the superior endplate of L2 and the superior endplate of the sacrum (S1) on the mid-sagittal image, as preciously described [70]. The lumbar angle is illustrated in Figure 17.

STUDY 2: Results

MRI degenerative findings such as disc bulging, protrusion, extrusion, HIZ, and annular tears were frequent in both groups, and only the frequency of disc bulging and total lumbar disc degeneration score was significantly higher in patients compared with the controls. End-plate findings (i.e., Modic changes and Schmorl's nodes) and spinal canal findings (i.e., spondylolisthesis and spinal stenosis) were frequent with no differences between groups. The lumbar lordosis angle in the patients was significantly smaller (less lordotic) than in the controls in both the supine and standing position. Despite this, the change in the lordosis angle (LA) from supine to standing position (ΔLA) was the same in both groups. This can be seen in details in Table 8.

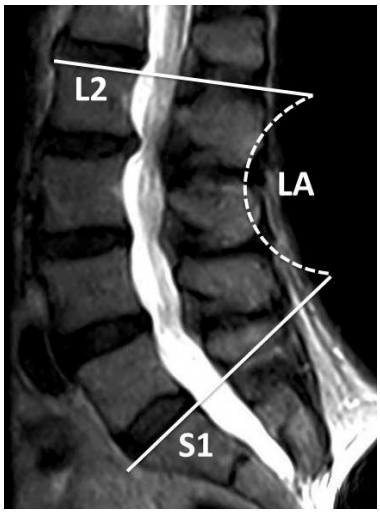

Figure 17. The lumbar lordosis angle measurement.

The lumbar disc degeneration score increased significantly with age by 0.08 score-points per year in the patient group and 0.06 score-points per year in the control group (adjusted for sex, VAS during activities, and VAS in rest) (Figure 18D). The lumbar lordosis angle was not associated with the lumbar disc degeneration score in either the supine or the standing position (Table 9, Figure 18 A-B) The change in lordosis (ΔLA) was negatively associated with the lumbar disc degeneration score in the healthy controls and remained significant after adjustments for gender and age. However, this association was not observed in the patient group (Table 9, Figure 18C).

Table 8.
Lumbar lordosis angle by groups.

	Patients N=38	Controls N=38	Difference between groups (95% Confidence Interval)		P-value
LA standing, mean (SD)	52.4° (11.4)	58.0° (10.3)	MD=-5.6	(-10.7 to -0.7)	0.027
LA supine, mean (SD)	45.6° (12.4)	52.0° (9.5)	MD=-6.4	(-11.4 to -1.3)	0.014
ΔLA, mean (SD)	6.8° (6.0)	6.0° (5.3)	MD= 0.8	(-1.8 to 3.3)	0.57

LA = lumbar lordosis angle and ΔLA (change in lordosis) = LA standing minus LA supine. Continuous data: presented as the difference between means (MD) and analysed using two-sample t-test assuming an unequal variance by default.

Table 9.
Univariable and multivariable regression presenting lumbar disc degeneration score as explanatory for the lumbar lordosis.

	Patients				Controls			
	Crude		Adjusted**		Crude		Adjusted*	
	βcoefficient (95% CI) r^2	P	βcoefficient (95% CI) r^2	P	β-coefficient (95% CI) r^2	P	βcoefficient (95% CI) r^2	P
LA stand	β = -1.3 (-3.6 to 1.1) r^2 = 0.03	0.28	β = -1.0 (-3.7to 1.7) r^2= 0.21	0.46	β = -1.08 (-3.9 to 1.8) r^2=0.01	0.45	β = -1.44 (-5.5 to 2.4) r^2=0.05	0.45
LA Supine	β = -0.61 (-3.2 to 2.0) r^2 = 0.00	0.64	β = - 0.33 (-3.3to 2.7) r^2=0.20	0.82	β = 1.36 (-1.29 to 4.0) r^2=0.03	0.30	β 1.22 (-2.4 to 4.8) r^2=0.04	0.49
ΔLA	β = -0.66 (-1.9 to 0.6) r^2= 0.03	0.28	β = -0.73 (-2.3to 0.9) r^2= 0.07	0.38	β = -2.43 (-3.7 to -1.2) r^2= 0.3	<.00	β = -2.66 (-1.0to–4.3) r^2= 0.36	.002

LA = lumbar lordosis angle; ΔLA = supine-to-standing lordosis change; LDD = lumbar disc degeneration score; β-coefficient = Regression coefficient (Lumbar lordosis angle, degree per Pfirrmann LDD score); 95% CI = 95% confidence intervals; r^2 =R-square; *adjusted for gender, age and pain during resting (VAS rest) and activities (VAS active). **adjusted for gender, age and pain during resting and activities (VAS rest).

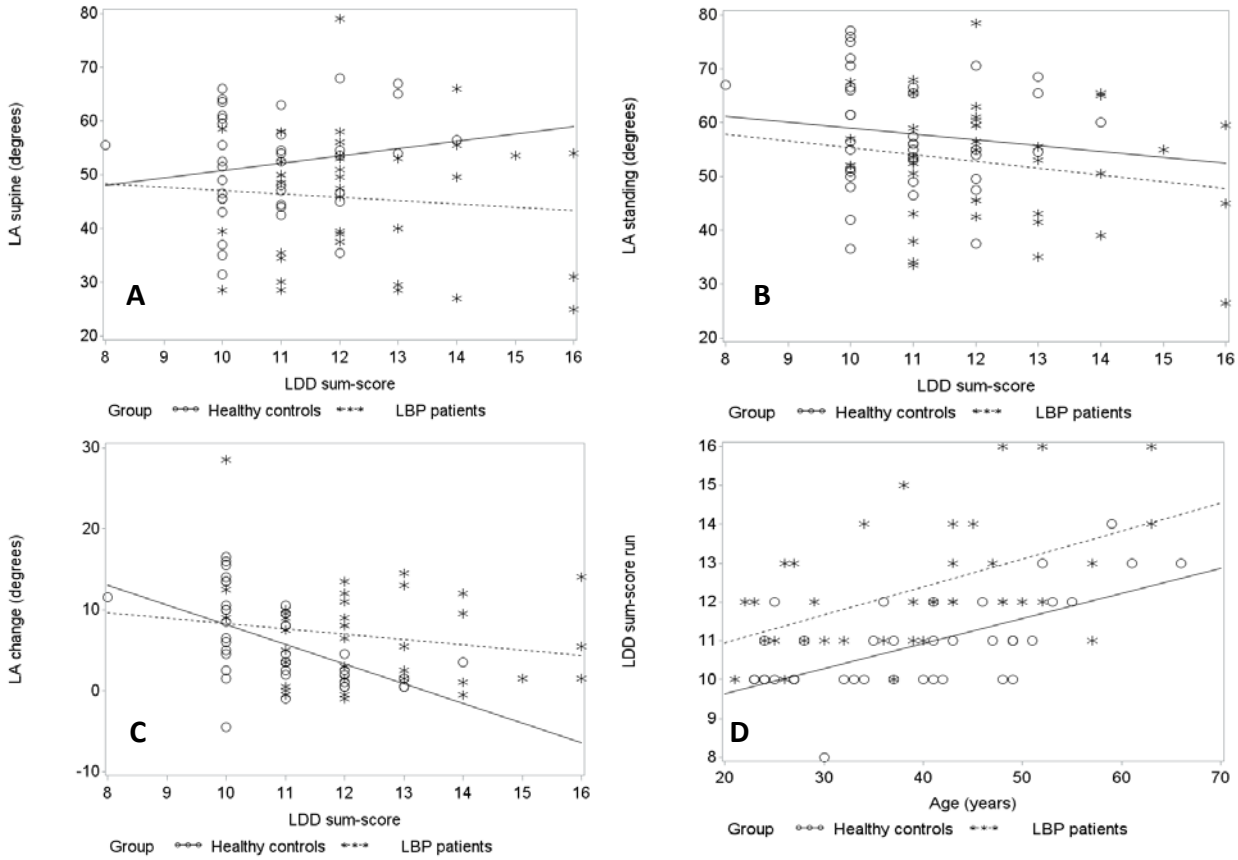

Figure 18. Association between lumbar disc degeneration score and (A) the lumbar lordosis in standing position, (B) the lumbar lordosis in the supine position, (C) the lumbar lordosis change. (D) The association between age and the disc degeneration LDD score.

STUDY 2: DISCUSSION

Principal finding

The changes in lumbar lordosis angle (ΔLA) between the conventional supine and standing position was independent of pain and the degenerative disc score in patients with severe back pain. This fnding is important, as the lumbar extension during standing pMRI may also be an essential contributor to dynamic changes of clinically relevant degenerative MRI findings in patients with low back pain.

Strength and limitations of the study

This study is the first comparing dynamic changes in the lumbar spine during standing pMRI in healthy individuals and patients with "severe" low back pain (i.e. VAS > 40mm during activities and rest), which is a major strength of the study, as patients with less severe back pain would have an extensive overlap with healthy individuals.

The Cobb method (or a modified Cobb method) was used for the possibility of comparing our result to other pMRI studies. This may represent a limitation, as two spinal curvatures of different magnitudes theoretically may result in the same Cobb angle [134]. This is illustrated in **Figure 19.** This issue could have been addressed by measuring the lumbar curvature, sacral angle and/or intervertebral angles.

Perspectives and future research

The association between the lumbar degenerative disc score and age indicated ''age-related'' disc degeneration in both groups, and hereby support the notion that degenerative disc changes are common in healthy individuals [19,23,35,73,75,118]. However, the higher overall mean lumbar degenerative disc scores found in the patients in all age groups supports the presence of a ''LBP-related'' lumbar disc degeneration. Advanced MRI mapping method such as T2-mapping MRI [53,135–138], T1rho MRI [139–141], dGEMRIC (Delayed Gadolinium-Enhanced MRI of Cartilage) [142] Spectroscopy (NMR) [143,144], Sodium MRI [145,146] and contrast enhanced imaging for degenerative inflammation [147–149] may have the potential of identifying the characteristics of this "LBP-related'' disc degeneration and hereby identify the origin of the back pain. These new MRI techniques may also allow a future subgrouping of patients by distinguishing painful degenerative changes from age-related changes in the disc [149].

"Age-related" disc degeneration was negatively associated with the change in lordosis (ΔLA), indicating a reduced compliance (back-stiffness) caused by the degeneration. Surprisingly, this was not found in the low back pain patients, and therefore "LBP-related" disc degeneration may have a different biomechanical phenotype. These results add evidence to the Kirkaldy-Willis three-phase degeneration theory, in which the second phase (i.e. the instability phase) is believed to be associated with back pain [150]. Longitudinal follow-up studies based on these pMRI findings are needed to confirm such an association.

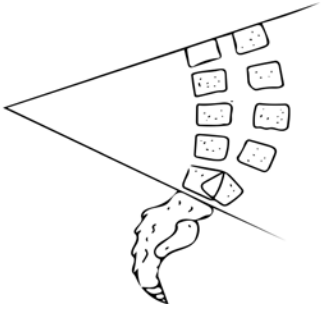

Figure 19. The figure shows that spinal curvatures of different magnitudes may result in the same Cobb angle. Inspired by Been et al. [134].

As previously discussed, studies have indicated that the conventional supine position with a pillow under the legs may cause an underestimation of spinal stenosis. We have conducted a study with the aim of investigating if adding a lumbar pillow in the supine position during conventional MRI can increase the precision of lumbar spinal stenosis? See a patient with the lumbar pillow in **Figure 20.** The study has indicated that standing pMRI is superior compared to MRI in the supine position with a lumbar pillow. The study has been published in Spine [151]. We are also collecting data for a similar study including 60 patients with a disc herniation.

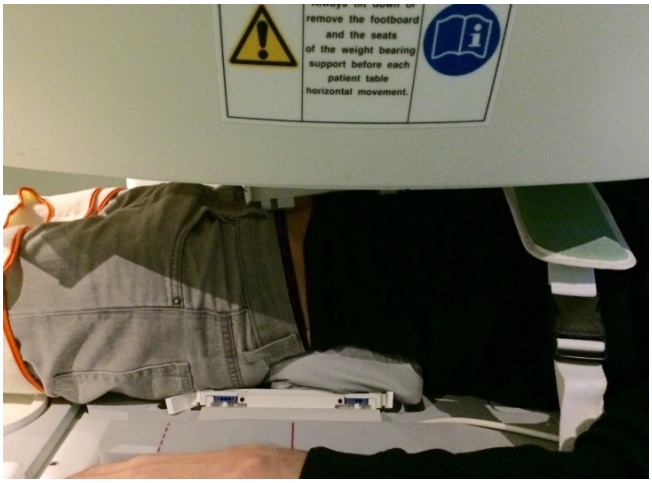

Figure 20. Demonstrates the positioning of the patients suspected of spinal stenosis in the supine position with extended legs and a lumbar pillow.

STUDY 3*:* BACKGROUND

Prior to the introduction of standing pMRI in the diagnostic of low back pain, it is important to know the reproducibility of potential dynamic MRI findings. The aim of this study was to assess the inter-observer and intra-observer reliability and absolute agreeent between three radiologists evaluating pMRI findings and positional changes in the lumbar spine.

STUDY 3: METHODS

One radiologist (ZR) with several years of experience interpreting MRI of the spine, one neuro-radiologist (AC) and one junior radiologist (CT) individually scored the MR images for degenerative findings known to potentially change from the supine to the standing position, i.e., herniation, spinal stenosis, spondylolisthesis, HIZ, facet joint effusion and juxtafacet cysts. Described in details in **Table 4.** To test dynamic alteration within the degenerative findings, the assessment included a validated semi-quantitative grading system for three of the degenerative findings, i.e., herniation, nerve compression, foraminal stenosis and spinal stenosis - described in details in **Table 5**. The supine and standing images were evaluated as one examination as recommended by the scanner's manufacturer. If a finding was achieved by positional change from the supine to the standing position this was reported separately. A subsample of 20 cases was reevaluated after two months by all radiologists for the assessment of intra-reader reliability.

STUDY 3: RESULTS

Seventy-five patients accepted participation and the full enrolment can be seen in **Figure 12**. A total of 56 patients were included, and 20 random selected cases were read twice**.** All readers agreed that in two confidence intervals and absolute agreement for each reader are shown in **Table 11 and 12**.

STUDY 3: DISCUSSION

Principal finding

Despite different levels of familiarity with pMRI, the three radiologists' readings showed a fair to substantial inter- and intra-reliability and high absolute agreement for all degenerative MRI findings and the semi-quantitative grading. This finding is important, as it shows that standing pMRI has a sufficient reliability to potentially be used as predictors of clinical prognoses and outcomes. There was a considerable difference in the number of positional changes reported by each radiologist, and the inter- and intra-reader reliability of positional changes were lower than the average pMRI reliability. This indicates that positional changes between the supine and standing position as an independent diagnostic outcome should be interpreted with caution for radiologists without special training. A high absolute agreement was found due to the large number of levels without any positional change from the supine to the standing position.

Strength and limitations of the study

Several studies have assessed the reliability of lumbar degenerative findings of patients in conventional MRI [70,72,152–154]. However, this is the first study to test the reliability of standing pMRI and positional changes from the supine to the standing position in lumbar degenerative findings.

This study is limited by the inclusion of a rather heterogeneous group including both patients with or without sciatica. However, it is likely that patients with advanced radiculopathy may have limited potential for dynamic changes in their degenerative findings, as the patient may keep their back in a forced position to reduce pain. This consideration was also discussed in study 2 [118]. Also, from a clinical perspective, it makes little sense to offer patients with a clearly detectable diagnosis on conventional MRI an additional standing pMRI scanning. The typical low back pain patient referred to standing pMRI will very likely have non-specific symptoms. Another limitation of this study is the effort of covering all the degenerative findings with a dynamic potential. Hereby, the sample size of each outcomes becomes relatively small, which explains the rather large confidence intervals for each Kappa-value. Ideally, the patients should be included based on a previous MRI, as this would have ensured larger numbers of each outcome. Furthermore, this would have enabled testing the reliability of positional changes for each degenerative finding.

Perspectives and future research

Despite a fair to substantial inter- and intra-reliability, the rating for the majority of the standing pMRI findings was not perfect. Having a reliable way to assess a predictive parameter across different readers is important for the daily clinical practise; therefore, training and consensus reading are needed, especially for assessing positional changes from the supine to the standing position. For that purpose, a teaching atlas has been produced (**Appendix**) and will be available for radiologists evaluating standing pMRI in our department and for future studies.

There are currently no international evidence-based recommendations for the use of standing pMRI, and the existing knowledge about how positional changes in current degenerative findings can be interpreted into a clinical context is limited. Therefore, standing pMRI must be regarded as an add-on examination to the conventional MRI [149]. The existing literature appears to have a lesser focus on the diagnostic precision or specificity of the addi-

tional findings' relationship with clinical symptoms and/or treatment effects [71,81,83,84,87,89,90,93,103,104,108]. Authors often consider a new technology "superior" if it identified pathology not detected by the conventional method. However, a higher sensitivity for degenerative findings on MRI seems irrelevant in a clinical context as the relationships between MRI findings, clinical history, and patient outcome are still controversial [12,19,59]. As previously mentioned, it is a well-known fact that degenerative findings are very common in individuals with and without low back pain [19,23,35,73,75,118]. It is therefore of concern that standing pMRI of the lumbar spine produces more false positive findings, which do not reflect underlying pain-inducing disease mechanisms [155]. To complicate matters, the liberal use of imaging in low back pain may even worsen long-term outcomes in some patients [156]. Therefore, studies reporting outcomes beyond anatomical changes are needed before standing pMRI of the lumbar spine can be regarded as providing a higher diagnostic specificity or additional benefit to low back pain patients. These considerations have been discussed in details in a review in Best Practise & Research Clinical Rheumatology [149].

To address some of the considerations discussed above, we have scanned over 250 consecutive low back pain patients with relevant radiculopathy while no signs of nerve root involvement on conventional supine high-field MRI have been found. In this study, the gold standard is represented by the patient symptoms and several standardised questionnaires. (Data handling under progress) However, the most valid evidence regarding the impact of a diagnostic test can be obtained from RCTs or longitudinal follow-up studies. Therefore, we have also conducted an RCT using standing pMRI findings as an explanatory outcome for an occupational medicine intervention programme. We have enrolled over 300 patients with difficulty in maintaining physically demanding jobs due to low back pain. All patients had a standing pMRI as part of their baseline assessment and a follow-up scan after one year. The GOBACK study has a dedicated homepage www.goback.dk, is registered on ClinicalTrials.gov (identifier: NCT02015572) and the study protocol has been published in the journal Trials to increase transparency [157]. The GOBACK study will give a unique opportunity to evaluate the potential long-term impact of standing pMRI on clinical outcomes. Furthermore, the study can explore the diversity of these imaging findings and link these to specific questionnaire profiles, thereby establishing new imaging-derived diagnoses or patient subgroups. (Manuscript on baseline data and six-month follow-up data is under preparation for publication).

Further Perspectives for G-Scan

G-scan has the potential to increase our understanding of other weight-bearing joints and positional changes in other anatomies. The MRI-system (G-scan) also allows imaging of the foot, ankle, knee and hip in both the supine and the standing position. See a volunteer's foot being imaged in the standing position in **Figure 21.** In MRI, isotropic three-dimensional (3D) sequences permit assessment of a structure of interest in any anatomical plane and from this, a 3D model can be built. This allowed us to test movements in the navicular bone height and medial navicular position in more than one dimension when changing from the unloaded (supine position) to the loaded foot (standing position). Reproducibility data has been published [158]

It is well known that the upright position affects the intracranial hydrodynamics and cerebral hemodynamics [82,159]. Therefore, it can be possible to quantify changes in CSF flows between different positions. The volume ventricular system and intracerebral dimensions have been measured in a pre-study. Preliminary assessments can be seen in **Figure 22.**

Table 10.
Number of degenerative findings, grades and positional changes of the standing pMRI.

	Reader A		Reader B		Reader C	
Findings	No	Change	No	Change	No	Change
Herniation type						
Protrusion	33	0	42	0	46	0
Extrusion	3	0	3	0	7	0
Bulging	58	0	74	0	46	0
Spinal stenosis	7	1	16	3	6	3
Spondylolisthesis						
Anterior	9	0	7	0	8	0
Posterior	3	0	7	0	2	0
HIZ	20	2	23	2	16	2
Facet joint effusion*	59	0	56	4§	33	8§
Juxtafacet cysts	0	0	0	0	0	0
Herniation nerve compression						
Grade 0	163	0	162	0	167	0
Grade 1	48	1	49	2	42	0
Grade 2	10	3	12	6	12	4
Grade 3	3	0	1	0	3	0
Foraminal Stenosis *						
Grade 0	351	0	347	0	281	0
Grade 1	64	5	86	5	146	25
Grade 2	31	2	14	7	16	6
Grade 3	2	2	1	1	5	1
Spinal stenosis						
Grade 0	163	0	131	0	181	0
Grade 1	53	0	77	5	37	2
Grade 2	6	1	14	4	4	2
Grade 3	2	0	2	0	2	0
Positional changes, total		17		39		53

The standing pMRI grading includes 224 disc levels (4 levels in each of the 56 patients) and in case the finding or grad was archived by a change from the supine to the standing position it was reported as a positional changes. *The total number of foraminal stenosis was 448 as the radiologists evaluated each side independently. §Facet joint effusion was the only positional change outcome to disappear in the standing position. HIZ = High Intensity Zone. Change = Positional changes between supine and standing

Table 11.
Inter-reader reliability and absolute agreement of the standing pMRI outcomes and positional changes from the supine to the standing position

	Reader A vs. B	Reader A vs. C	Reader B vs. C	Average
	κ (95% CI) [Agreement in %]	κ (95% CI) [Agreement in %]	κ (95% CI) [Agreement in %]	κ (95% CI) [Agreement in %]
Herniation type	0.71 (0.63 to 0.79) [82.5%]	0.81 (0.75 to 0.88) [88.8%]	0.66 (0.58 to 0.74) [78.6%]	0.73 (0.66 to 0.79) [86.2%]
Spinal stenosis	0.50 (0.25 to 0.75) [95.1%]	0.60 (0.29 to 0.92) [97.8%]	0.52 (0.27 to 0.78) [95.5%]	0.54 (0.44 to 0.63) [96.2%]
Spondylolisthesis	0.68 (0.46 to 0.89) [96.4%]	0.76 (0.57 to 0.96) [99.1%]	0.69 (0.49 to 0.90) [96.9%]	0.71 (0.64 to 0.76) [97.0%]
HIZ	0.82 (0.69 to 0.95) [96.9%]	0.76 (0.60 to 0.92) [96.4%]	0.80 (0.66 to 0.94) [96.9%]	0.79 (0.74 to 0.83) [96.7%]
Facet joint effusion*	0.63 (0.52 to 0.74) [91.7%]	0.56 (0.44 to 0.69) [92.0%]	0.64 (0.52 to 0.76) [93.5%]	0.61 (0.54 to 0.66) [92.4%]
Herniation nerve compression grade	0.70 (0.60 to 0.79) [86.1%]	0.73 (0.64 to 0.82) [87.5%]	0.68 (0.59 to 0.78) [84.8%]	0.70 (0.63 to 0.76) [84.8%]
Foraminal Stenosis grade*	0.71 (0.66 to 0.78) [87.5%]	0.53 (0.46 to 0.60) [75.4%]	0.57 (0.49 to 0.64) [78.8%]	0.60 (0.54 to 0.66) [80.6%]
Spinal stenosis grade	0.62 (0.52 to 0.71) [78.1%]	0.69 (0.59 to 0.8) [87.1%]	0.47 (0.37 to 0.58) [72.3%]	0.59 (0.49 to 0.66) [79.2%]
Positional changes**	0.40 (0.25 to 0.55) [98.3%]	0.27 (0.14 to 0.40) [97.5%]	0.34 (0.22 to 0.46) [97.0%]	0.34 (0.30 to 0.38) [97.6%]

Inter-reader reliability by using κ statistics (dichotomy data) or weighted κ statistics (ordinal data) and based on 56 MRI examination cases finding include all L2/L3 to L5/S1 intervertebral disc levels. Numbers in parentheses are 95% confidence intervals (95% CI) and absolute agreement in squared parentheses [Agreement in %]. HIZ = Hyper Intense Zone. * Based 224 x 2 facet joints. **Includes all outcomes

Table 12.
Intra-reader reliability and absolute agreement of the MRI outcomes

	Reader A	**Reader B**	**Reader C**	**Average**
	κ (95% CI) [Agreement in %]	κ (95% CI) [Agreement in %]	κ (95% CI) [Agreement in %]	κ (95% CI) [Agreement in %]
Herniation type	0.52 (0.36 to 0.68) [75.0%]	0.40 (0.25 to 0.57) [62.5%]	0.72 (0.59 to 0.85) [83.8%]	0.54 (0.37 to 0.68) [73.8%]
Spinal stenosis	0.75 (0.52 to 0.98) [95.0%]	0.59 (0.37 to 0.81) [87.5%]	0.51 (0.16 to 0.88) [93.8%]	0.61 (0.45 to 0.73) [92.1%]
Spondylolisthesis	0.85 (0.56 to 1.00) [98.8%]	0.85 (0.56 to 1.00) [98.8%]	0.85 (0.56 to 1.00) [98.8%]	0.85 (0.77 to 0.90) [98.8%]
HIZ	0.48 (0.03 to 0.91) [95.3%]	0.78 (0.54 to 1.00) [96.3%]	0.51 0.14 to 0.88) [93.8%]	0.59 (0.42 to 0.71) [95.0%]
Facet joint effusion*	0.49 (0.25 to 0.72) [91.3%]	0.36 (0.14 to 0.59) [88.1%]	0.67 (0.29 to 1.00) [98.1%]	0.61 (0.50 to 0.70) [92.5%]
Herniation nerve compression grade	0.74 (0.58 to 0.89) [87.5%]	0.71 (0.50 to 0.91) [88.8%]	0.80 (0.64 to 0.97) [97.0%]	0.75 (0.64 to 0.83) [89.6%]
Foraminal Stenosis grade*	0.60 (0.33 to 0.57) [83.8%]	0.56 (0.37 to 0.75) [80.6%]	0.64 (0.53 to 0.75) [80.6%]	0.60 (0.56 to 0.74) [84.2%]
Spinal stenosis grade	0.81 (0.65 to 0.97) [92.5%]	0.50 (0.32 to 0.68) [68.8%]	0.68 (0.39 to 0.97) [92.5%]	0.66 (0.52 to 0.77) [84.6%]
Positional changes**	0.52 (0.22 to 0.83) [99.1%]	0.25 (0.06 to 0.44) [96.6%]	0.35 (0.16 to 0.55) [97.0%]	0.34 (0.28 to 0.40) [97.6%]

Intra-reader reliability by using κ statistics (dichotomy data) or weighted κ statistics (ordinal data) and based on 56 MRI examination cases finding include all L2/L3 to L5/S1 intervertebral disc levels. Numbers in parentheses are 95% confidence intervals (95% CI) and absolute agreement in squared parentheses [Agreement in %]. HIZ = Hyper Intense Zone. * Based 224 x 2 facet joints. ** Includes all outcomes.

CONCLUSION

A substantial risk of fainting (orthostatic syncope) during the standing scan was almost eliminated. The ability to increase the lumbar lordosis during standing pMRI was not affected by severe back pain or advanced lumbar disc degeneration in low back pain patients. The reproducibility of standing pMRI was fair to substential, although the ability to detect positional between supine and standing position was less reliable.

There are currently no international evidence-based recommendations for the use of standing pMRI, and we have little knowledge about how to interpret these positional changes in the lumbar spine into a clinical context. Nevertheless, standing pMRI of the lumbar spine may add a valuable diagnostic for patients suspected of nerve root compression with associated leg pain, or for patients with worsening lumbar back pain in the upright position, although this is not clarified. Therefore, further research is warranted to test the precision (sensitivity and specificity). Until then, weight-bearing MRI must still be seen as an add-on examination to the conventional MRI evaluation.

ABBREVIATIONS

Anti-TNF-α	Anti-Tumour Necrosis Factor α
CI	Confidence Intervals
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DCSA	Dural Sac Cross-sectional Area
DCSD	Dural Sac Cross-sectional Diameters
DVT	Deep Vein Thrombosis
FOV	Field of View
GAGs	Glycosaminoglycans
GRE	Gradient Echo
ICC	Inter Class Coefficient
kMRI	kinematic Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
OECD	Organization for Economic Co-operation and Development
pMRI	positional Magnetic Resonance Imaging
PRO	Patient Reported Outcome
RCT	Randomised Controlled Trial
SCCA	Spinal Canal Cross-sectional Area
STIR	Short Tau Inversion Recovery
T	Tesla
TSE	Turbo Spin Echo
T1w	T1-weighted
T2w	T2-weighted
VAS	Visual Analogue Scale

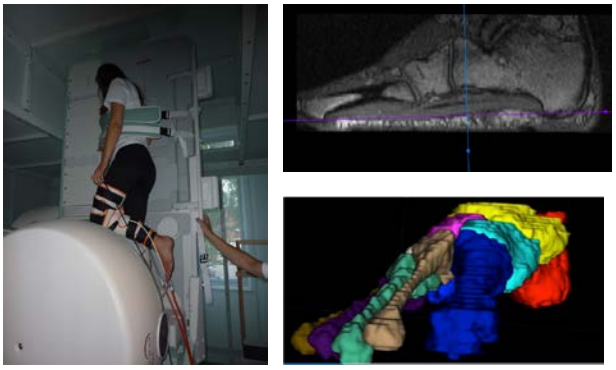

Figure 21. A patient is scanned in the standing position (Above) The images below demonstrates the 3D model of the foot in the unloaded position (collar images) and mid- sagittal image in the loaded position (black and white) of a standing patient.

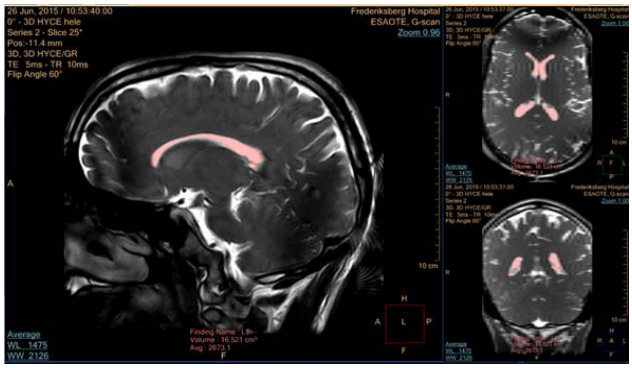

Figure 22. A participant in the upright seated position (left) and the measurement of the brain's ventricular system (right)

SUMMARY

This PhD thesis is based on three scientific papers. In 2011 the Parker Institute the department of rheumatology introduced standing weight-bearing MRI (G-Scan, ESAOTE, Genova, Italy) in the diagnostic of low back pain patients. Unfortunately, we experienced a substantial risk of fainting (orthostatic syncope) during standing pMRI. In paper 1 we present in an observational study that the risk of fainting (19%) during standing pMRI could almost be eliminated by the use of an external pneumatic compression device (2%). The lumbar lordosis in the standing position is a significant contributor to positional changes in the morphology in the lumbar spine. In paper 2, we present in an observational study that changes in lumbar lordosis angle (ΔLA) between the conventional supine and standing position were independent of pain and the degenerative disc score. Before a full introduction of standing pMRI in clinical practice, it is important to know if the interpretation of positional changes in common degenerative findings has a sufficient reproducibility. In **paper 3**, we present in a reliability study that the pMRI evaluation has a fair to substantial reliability, although positional changes in the lumbar spine's morphology from the supine to the standing seems a less reliable outcome.

There are currently no international evidence-based recommendations for the use of standing pMRI, and we have limited knowledge about how to interpret these positional changes in the lumbar spine into a clinical context. Therefore, further research is warranted to test the precision (sensitivity and specificity) in prospective longitudinal studies or RCTs. However, from a clinical perspective it seems logical to scan patients with low back pain in the position worsening their symptoms – typically the upright position. Therefore, standing pMRI may provide a higher diagnostic specificity and additional benefit to low back pain patients in the future.

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