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On Lumbar Disc Herniation

– Aspects of outcome after surgical treatment

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Stockholm 2017

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On Lumbar Disc Herniation

– Aspects of outcome after surgical treatment

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Stockholm 2017

To

my dear family,

all patients suffering from sciatic pain and

all patients who have contributed with data in this project.

CONTENT

1 ABSTRACT

Knowledge about sciatica has grown immensely since the days of Hippocrates. Even so one must be impressed with the anatomical insights of those ancient times. Today we are able to describe at a molecular level how the intervertebral disc degenerates and how a herniation is evolved and its physical consequences for the patient. It is now possible, at least partially, to follow the impact a herniation creates on the compressed nerve root, the course of the pain impulses through all modifying systems, up to the brain – and yet not understand the reaction it may cause in that patient! There are still many, many knowledge gaps that need to be filled!

Study I*:* Outcome after surgery for *children and adolescents* was studied in the Swedish national spine register, Swespine, compared to adults 19-39 and older than 40 years. Children and adolescents were more satisfied with the surgical treatment than adult groups and there was a slight deterioration of outcome by age.

Study II*:* Patients admitted to hospital and surgery *non-electively*, via the emergency ward, were compared to electively operated patients. At baseline the non-elective group, reported more pain, dysfunction and poorer quality of life, but after surgery all outcome values were almost equal, adjusted or not.

Study III*: Inflammation* around the nerve root is an important factor in the pain elicited by disc herniation. The level of inflammation measured in serum with C-reactive protein before surgery was however not associated with outcome in a prospective study of 177 patients. On the other hand, 'Plasminogen Activator Inhibitor 1' (PAI-1), an important factor in *fibrinolysis* and scar modulation, was to some extent associated to poor outcome in the same cohort of patients. The exact reason for this association is not clear. It may be hypothesized that hypo-fibrinolysis is associated with excessive scar formation.

Study IV: This thesis has used data from *Swespine*. The *validity* of these data may be questioned, as a fairly large proportion of patients are lost to follow-up. In an attempt to define if the loss to follow-up has an impact on the interpretation of data from Swespine, a comparison was made with a single-center study with very few patients lost to follow-up. There were some minor baseline differences between the groups, but outcome at 1 and 2 years, was almost equal in all used variables. These data indicate that non-responders in Swespine may be considered lost at random and would not influence the interpretation of data from Swespine.

2 LIST OF SCIENTIFIC PAPERS

I. ***An observational study on the outcome after surgery for lumbar disc herniation in adolescents compared with adults based on the Swedish Spine Register.***
Lagerbäck T, Elkan P, Möller H, Grauers A, Diarbakerli E, Gerdhem P.
Spine J. 2015 Jun 1;15(6):1241-7. doi: 10.1016/j.spinee.2015.02.024.
PMID: 25701544

II. ***Similar results after non-elective and elective surgery for lumbar disc herniation: an observational study based on the SweSpine register.***
Elkan P, Sjövie Hasserius J, Gerdhem P.
Eur Spine J. 2016 May;25(5):1460-6. doi: 10.1007/s00586-016-4419-2.
PMID: 26849140

III. ***Markers of inflammation and fibrinolysis in relation to outcome after surgery for lumbar disc herniation. A prospective study on 177 patients.***
Elkan P, Sten-Linder M, Hedlund R, Willers U, Ponzer S, Gerdhem P.
Eur Spine J. 2016 Jan;25(1):186-91. doi: 10.1007/s00586-015-3998-7.
PMID: 25962814

IV. ***Are results from a national register on surgery for lumbar disc herniation valid?***
Elkan P, Lagerbäck T, Möller H, Gerdhem P.
Submitted

3 ABBREVIATIONS

A. D	After Christ
ANCOVA	ANalysis of CoVAriance
ASSR	American Society of Spine Radiologists
B.C	Before Christ
CGRP	Calcitonin Gene-Related Peptide
D-dimer	Is a fibrin degradation product
EQ-5D	Euro Quality of Life -5 Dimension Questionnaire
GA	Global Assessment
hsCRP	high sensitive C-Reactive Protein
LDH	Lumbar Disc Herniation
LDHS	Lumbar Disc Herniation Study
Mb	Morbus (illness)
MCID	Minimal Clinical Important Difference
MMP's	Matrix MetalloProteinases
MRI	Magnetic Resonance Imaging
ODI	Oswestry Disability Index
OR	Odds Ratio
PAI-1	Plasminogen Activator Inhibitor 1
PROMs	Patient Reported Outcome Measures
ROC	Receiver Operating Characteristics
SF-36	Short Form 36
SPORT	Spine Patient Outcomes Research Trial
SPSS	Statistical Package for Social Sciences
VAS	Visual Analog Scale

4 BACKGROUND

4.1 A brief historical review

Back pain and sciatica has been known since ancient times. Early societies associated it with evil powers in nature. It was first with *Hippocrates* (460-370 B.C.), observations of nature in combination with logic reasoning as the ground for diagnosis, was applied as method. Thus, he has been called 'the founder of scientific medicine' [1]. He produced systematic, anatomical and pathological reviews especially of the skeleton, joints and spine. Effects of tuberculosis in different organs, including the spine, among other diagnoses is impressively described, considering they are 2,400 years old and would render him the title 'father of spine surgery' [1]. *Galen of Pergamum* (129-200 A.D.) was another Greek physician, but 500 years younger [2]. He was famous for his meticulous anatomic studies of the spinal cord, nerves and neurological effects of injuries to these at different levels. He based his knowledge on apes and pigs, and what remained of the gladiators' bodies after their fights. He was the first to describe the nervous system and its effects on muscles and skin sensation. As he also was Christian and thought his remarkable findings reflected the wisdom of God, his knowledge was accepted and survived into the Age of Enlightenment. A couple of hundred years after Galen, *Caelius Aurelianus* made a very well expressed clinical description of lumbago with sciatica, that might have been written today [3]. At this point one could say that the anatomical background as well as the clinical appearance were known and described, but not linked together in the understanding of the pathophysiological background of sciatica.

Not very much new knowledge was added through the centuries, until the 18th, when the scientific spirit of the Enlightenment Century started the revolution of knowledge, that brought us to where we are today. *Domenico Cotugno* in 1764, for the first time recognized radicular pain as coming from the sciatic nerve. Subsequently sciatica was called 'Cotugnos Disease'. 1857 the famous pathologist *Rudolf Virchow* examined disc pathology and described a disc herniation as a kind of tumor, 'Virchow's Tumor', but did not put it in connection with the nerve root and sciatica. The first reported excision of a disc herniation, was done in 1908 in Berlin, by *Feodor Krause*. When performing this operation, he removed the entire lamina of the spinal canal and the excision was performed through the dura sac. The patient was immediately relieved from pain after the surgery, but the removed tissue was thought to be an 'enchondroma'…

It was not until the beginning of the 30s, when *Mixter and Barr* presented 'ruptured intervertebral disc' as a source of sciatic pain [4]. On 29th of June 1932, at Massachusetts General Hospital, the neurosurgeon Jason Mixter operated on a 28-year man, with severe, intractable, left sided S1-sciatica after a ski accident earlier that year. He performed massive laminectomies from L2-S1, found and removed what he thought was the 'tumor' that compressed the left S1-root and sent it to pathological analysis. The patient was completely relieved of pain at discharge. The pathologist found nothing but normal cartilage in the specimen. The initially referring physician, Dr. Joseph Barr, knew there was an accident causing sciatica in this patient and did not believe in the 'theory of tumor'. Together with the pathologist they reviewed the specimens from some earlier operations on 'spinal enchondromas' operated by Dr. Mixter. When they only found normal disc tissue in these specimens too, their conclusion was clear; *most sciatica is caused by herniated disc tissue*.

Gathering 19 cases in the 'cornerstone' article from 1934, this idea begun to reach acceptance by time [5]. Anecdotally, the surgeon *Walter Dandy*, already in 1929 published his article on two cases with 'cauda equina syndrome' and realized the origin of the removed tissue as disc, but his findings never came to a wider acceptance [6, 7]. The evolution of disc surgery thereafter is presented in Paragraph 4.12 *Techniques*.

Simultaneously, to this described evolution in the understanding and knowledge about the somatic background to sciatica, a deep religious and philosophic struggle continued since ancient times, on the relationship between the human mind and body. A 'discussion' that during a long time, over 1,500 years, was hampered by religious dogma. Interestingly, the original cultures were prone to a perception of existence as an indivisible unit of mind and body (cf. Shamanism), much comparable to what we today would refer to as a 'holistic view', but without the superstitious elements. The 'Father of spine surgery', Hippocrates, thought that 'the whole unit of mind and body, was more than the single parts.

The origin of modern medicine is regarded to have started about 1850, when a more natural scientific approach reentered the medical development. Statistics and observational studies were used and a century of never before seen evolution on all human areas began. In this concept, the mind and the body 'met again' and were regarded as just two different aspects of the same entity. 'The nature can be *explained*, but the human being and the human existence must be *understood* and understood in its coherence', Carl-Magnus Stolt wrote in his book on 'Medicine and the Humaneness' [8]. This summarizes the holistic concept of today very well. Translating this to care of lumbar disc herniation, would mean that all relevant dimensions of a patient (including psychological and social) must be included in the evaluation. We cannot just measure MRI findings and angles of root tension signs, we must *communicate* with the patient to understand what is important and why. It may sound obvious but is yet very challenging and difficult…

4.2 Anatomy and function - normal

The human spine consists of 33 *vertebrae*; 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal. The 4 coccygeal vertebrae are fused, forming the tailbone and the 5 sacral, fused to form the sacrum, making a total of 26 individual bones. The sacrum articulates to L5, which like all other articulate to the cranial vertebra and most cranially, to the scull bone (Figure 1). The elements allowing movement between two vertebrae are the two *intervertebral joints* (facet joints) and the *intervertebral disc*. Two vertebrae and the disc between them, form a '*motion segment'*. The range of movements varies, but is highest in the cervical and lumbar spine and lowest in the thoracic, where the chest restricts the movements (Figure 2).

All motion segments contain a disc (except the 1st cervical). This is made up of glycosaminoglycans, collagen and elastin fibers, matrix proteins, a small amount of disc cells and mostly water, which together acts as a 'hydraulic load dampener', optimizing load dispersion and permits a certain amount of movement (cf. a silicone or rubber disc). The glycosaminoglycans, mainly 'aggrecan', have high affinity to water and regulates the water content. The amount of glycosaminoglycans (and hence water) is highest in the center of the disc, *nucleus pulposus* and decreases peripherally, where the collagen and a small amount of elastin fibers instead make a more solid and stable web like construction,

*annulus** *fibrosus* [9]. This is in the periphery forming an outer shell and strongly adapted to the vertebral edge.

Another very important part of the segment, is the *cartilage endplate* (Figure 3). In early childhood, it serves as the vertebral growth plate, richly vascularized and innervated. Already during the first years, the main vascularization through the endplates into the disc, has substantially disappeared [10]. The nutrition of the disc cells is after that depending on diffusion through the small canals left in the endplates after the vessels, but also from the still vascularized outer few millimeters of the annulus fibrosus. Thus, the main central part of the disc is the greatest avascularized organ of the adult body [10].

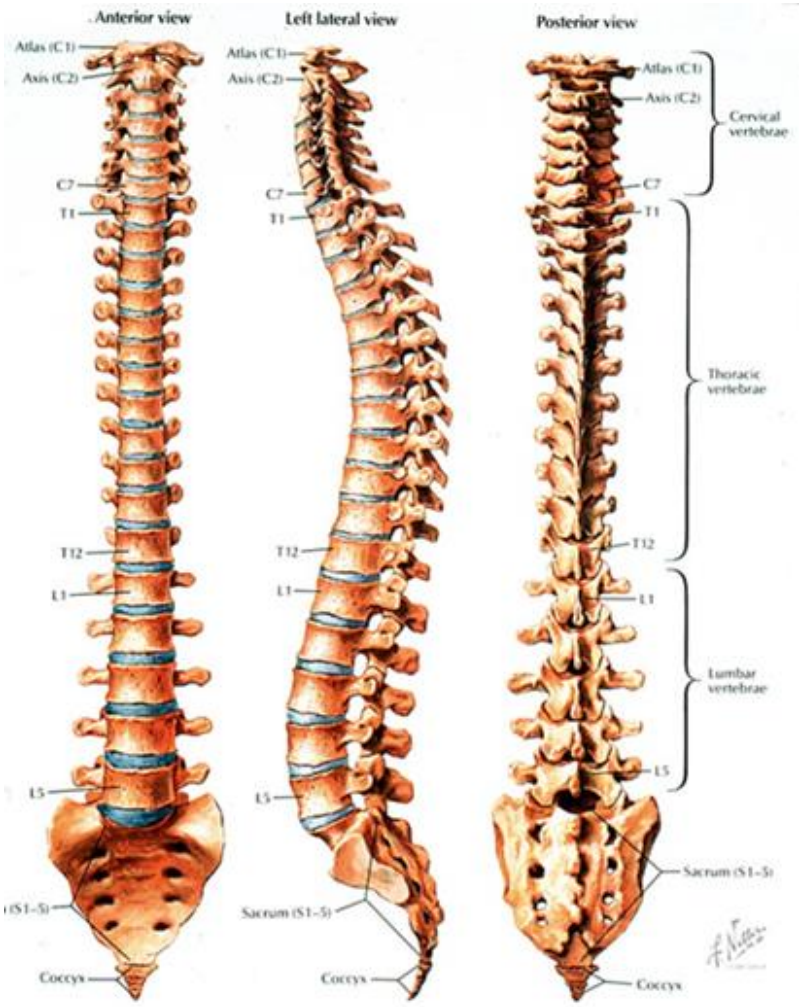


Figure 1. The human spine.

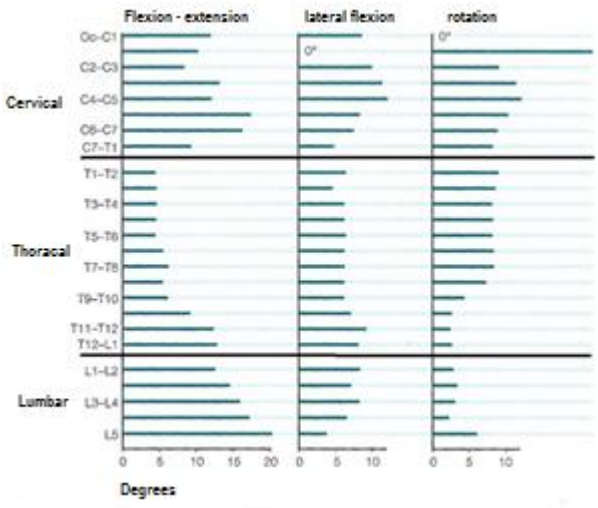


Figure 2. Range of movements.

The human spine is a construction originally aimed to serve quadromanous climbers. Since our ancestors began to rise on two legs, approximately 5-6 million years ago, the load on the human spine has changed totally, but the spine has almost remained the same [11].

This unique way of locomotion resulted in an array of advantages for mankind, but certainly also led to many, for human beings mostly unique problems, like foot, knee, hip and spinal degeneration, osteoporosis and a number of other problems according to Latimer [11].

* Annulus and anulus fibrosus are both seen and accepted in modern English, though anulus fibrosus would be the most correct form. Annus refers to ‘year’ and anus to ‘ring’ in Latin.

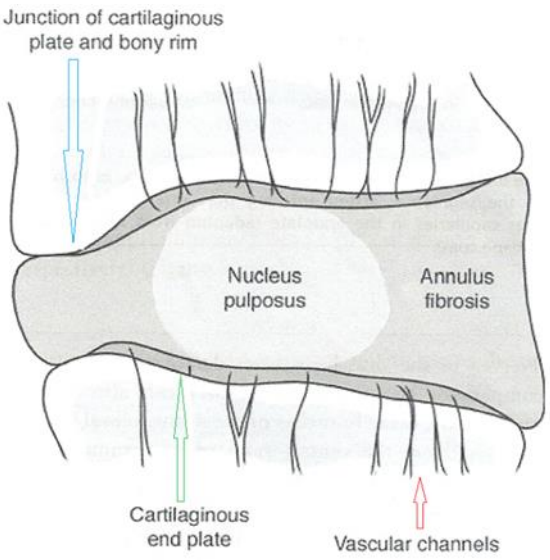


Figure 3. The vertebral endplate and nutrition.

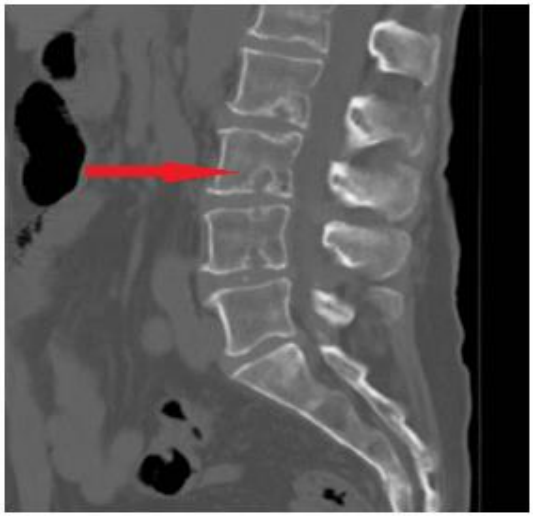


Figure 4. Schmorl's Noduli

Even so, some evolutionary driven developments did appear by time. The most important are
mentioned in their connection, further on in the text. Concerning the *vertebral shape*, small changes, as a result of bipedal evolution, has been discussed [12, 13]. Harington et al, showed that round endplates would create more load to the disc, compared to more elliptical forms, only by applying 'The law of Laplace' to the water-like disc. Plomp et al, accomplished computerized analyses of the shapes of the last thoracic or first lumbar vertebra from 'pathological' and 'healthy' humans, from chimpanzees and orangutans. They found a clear similarity between the shapes of 'pathological' human vertebrae and chimpanzee, implying that the evolutionary 'older shapes' in chimpanzees, correlated to 'pathological' findings in humans. 'Healthy' shapes of human vertebras, is a solely human finding, that cannot be found among other species and is characterized by larger foramina, long, narrow pedicles and more ovoid, 'heart-shaped' end-plates. The 'pathological', evolutionary older form of a vertebra, is rounder, thus supporting the earlier hypothesis by Harrington et al.

The classification of 'pathological or healthy' was in the above mentioned study based on findings of intra-vertebral disc herniations, 'Schmorl's Noduli'[14] (Figure 4). These are regarded as either genetical manifestations, or traumatically induced results of in- or extensive axial loads in the spine and cannot be found in our quadropedous ancestors [15].

4.3 Degeneration, pathophysiology - background

The human disc has like most other tissues in the body a continuous regeneration and a dynamic structure. The small number of cells, approximately 1% of the total volume, are able to produce new proteoglycans of different sorts, as well as some collagen fibers. On the other hand, a variety of enzymes; cathepsins, aggrecanases and matrix metalloproteinases (MMP's), are found and also produced in the disc. These enzymes are capable of breaking down various kinds of matrix molecules. The survival of a functional disc is relying on a healthy balance between these counteracting processes [9, 10].

The factors leading to disturbances of this balance has been discussed and three main causes have emerged, *nutritional*, *mechanical* and *genetical*.

4.3.1 Nutritional impact

The nutritional impact is obvious, as the blood supply to the disc is provided only by diffusion from capillaries in the small canals of the vertebral end-plates, or from the vascularized outer millimeters of the annulus fibrosus [9]. Any factor that affects the general blood supply, like arteriosclerosis [16], smoking [17], diabetes [18], and obesity [19], will impact the metabolism of the disc cell negatively. More recent research suggest that the transportation of metabolites that cross the end-plate *increases* with age, but that cell function despite this is *decreased*, maybe as a result of age induced cellular dysfunction [20].

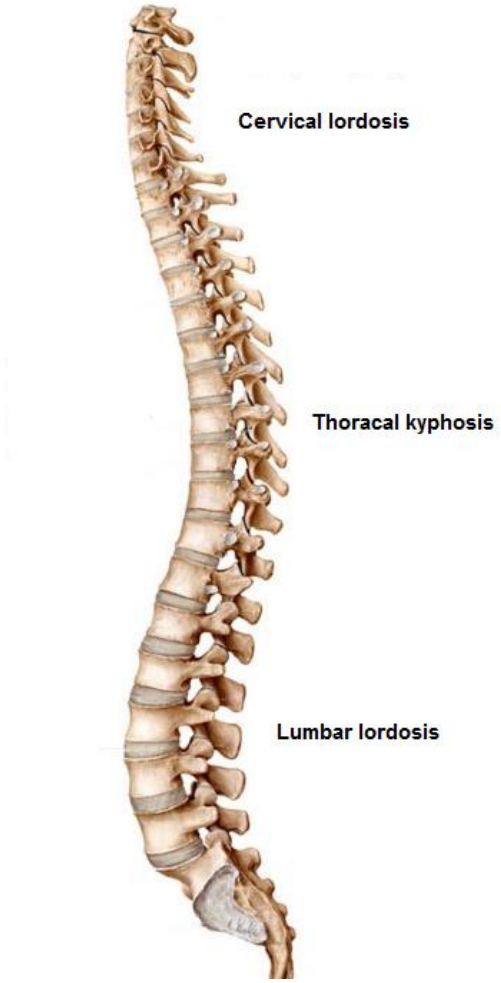


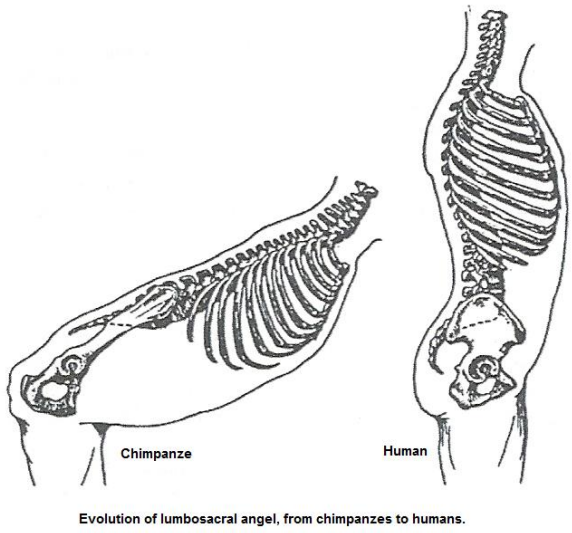
Figure 5. Sagittal balance and

4.3.2 Mechanical impact

Mechanical load in the spine, especially the lower lumbar part, are substantial and at least traumas and excessive loads, have since long been regarded as a factor inducing dysfunction. In upright position, the continuous forces at the L4-5 disc has *in vivo*, been measured to 200-550 Newton, forces that during more heavy loadings and positions (bending), easily can be ten-folded [21].

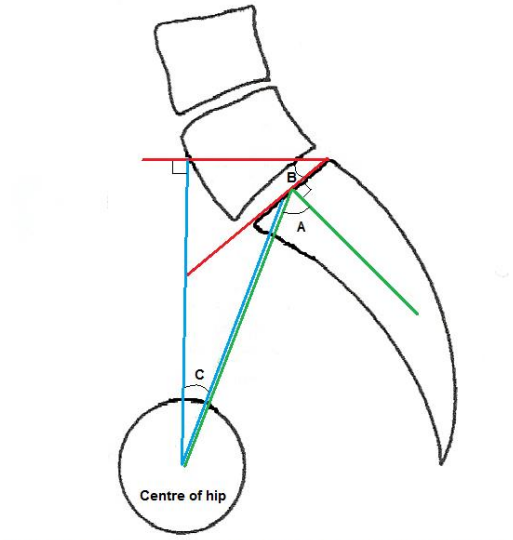
The bipedal evolution of mankind put high demands on the human spine. The higher loads on the weight bearing components of the spine, i.e. normally the disc and intervertebral joints, is mentioned above. The importance of keeping the body load above the pelvis, in optimal balance to minimize the efforts of being in upright position, is another demand [22]. Thus, the *spinal balance* had developed into great importance. The development of the *lumbar lordosis* is unique to the human spine [23]. (Figure 5). It seems to have developed during the same period of the evolution as human kind became bipedal.

Another great evolutionary change is that of *the pelvis* from its original almost flat form in the anthropoid apes, orientated in the same direction as the spine, to the more horizontal, bowl like support of the abdomen, that it forms in modern humans [22]. (Figure 6). The upper part of the sacrum (end-plate of S1) will form the fundament of the spine and is angled to the horizontal line to induce or compensate (what is primary is not known) for the lumbar lordosis, needed to facilitate the balance of the upright posture (Figure 5). Compensatory curves have evolved as the thoracic kyphosis and the cervical lordosis. This construction is in most human beings, during their first decades, optimally functional; balancing the upright posture, minimizing the body load of the spine and functioning as a shock absorber during gait and running [22, 23]. It also permits a considerable range of motion.



Evolution of lumbosacral angel, from chimpanzes to humans.

Figure 6. Evolution of the pelvis.



Pelvic parameters: A = pelvic incidence, B = lumbosacral angle (sacral slope), C = pelvic tilt (version).

Figure 7. Pelvic angles.

4.3.3 Genetical impact

Hereditary and genetical aspects have in the last 1-2 decades been proven to play a very important role in the development of disc generation, probably causing at least 50% or more of the variability of the disc degenerative process [24-27]. This item is further discussed under Paragraph 4.10 *Risk factors.*

4.4 Pathophysiology of disc degeneration - development

The water content decreases both with age and degeneration, about 20-30%, as the proteoglycans are reduced. This leads to a reduction of the osmotic pressure of the disc, with less capacity of weight bearing [9, 10]. The composition of collagen fibers is changed, resulting in more denatured fibers of poorer biological function. The disc begins to bulge around the outer border (annulus) and grows more fibrotic and fragile. When the disc gradually no longer functions with hydrostatical properties, the load is not dispersed optimally, resulting in local stress concentrations, giving microfractures in the endplates, matrix disorganization with fissures and tears of the annulus [9].

The locally very high loads on the endplates may also produce a local reaction, in the shape of inflammation and edema in the subchondral endplates [28]. The 'acute' inflammatory phase (type 1 changes), is after some time followed by a more inactive phase, characterized by fat-transformed bone marrow (type 2 changes). Finally, the process may end up in a fibrotic and sclerotic phase (type 3 changes). All three phases may be present at the same time though. These changes are initially described by de Roos et al [29], but it was Modic who made them known and by others called 'Modic changes', as they still are referred to [28]. Modic changes have been discussed extensively since they were described. Type 1 changes also seem to correlate to back pain [30] (Figure 8).

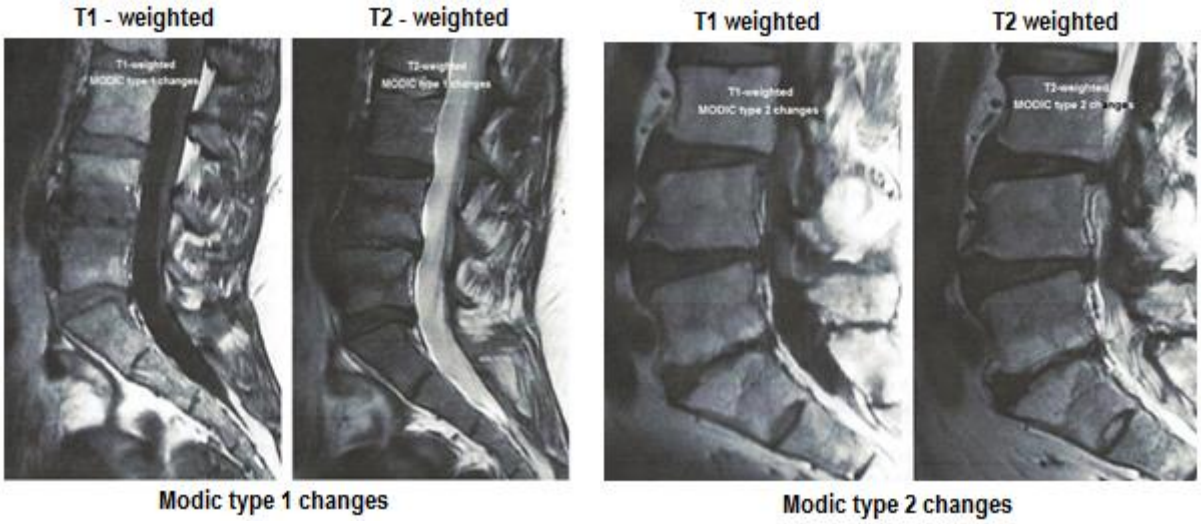


Figure 8. Modic changes

The above described development of patho-physiology has mostly been accepted, but during at least a decade several studies have reported the finding of bacteria in the disc (a low-virulent infection?), mainly caused by *Propionibacterium acnes* in patients with Modic changes and disc herniation [30-32]. Some authors have even reported clinical antibiotic treatment of this supposed infection, with improved result on low back pain [33]. The discussion on this controversy is still ongoing, but it seems as the findings are accepted per se, the etiology, their role in the development of Modic changes and the eventual symptoms and clinical relevance remain unclear [34, 35]. *Proliferation* of *cells* and *increased cell death* in the disc matrix, is also a characteristic finding in disc degeneration. These cells may still produce some collagen and aggrecan molecules (responsible for the keeping the hydrostatic pressure), but not as efficient as originally [20]. The matrix cells also produce several kinds of enzymes, responsible for breaking down the matrix molecules and a vicious circle may thus result. Another process seen during degeneration, is the *ingrowth of vascular*, and *neural fibers* into the disc [9]. If this is a 'normal' healing process, like anywhere else in the body, where injured tissue is present, or a more specific response to the altered biological structure of the degenerated disc, is not known. The ingrowth of nerves is proposed to be responsible for at least some of the chronic, unspecific pain, often noted in connection with degeneration of the spine [9].

The question of whether ‘normal aging’ and ‘pathological’ disc degeneration is the same, or different processes, is yet not solved. In fact, there are no signs of differences in pathophysiology or biology demonstrated so far [10, 36].

Others have reported disc degeneration being different processes. Adams et al [15], argue for two types; *‘Endplate-driven’* type in the thoracic and upper lumbar spine, consisting of endplate defects, Schmorl’s nodes and delamination, internal bulging and finally collapse of the annulus *into* the disc. This type has a high heredity, usually occurs before the age of 30 and presents only with moderate back pain. It is thought to be caused by spinal compression forces. The other type, *‘Annulus-driven’*, is most common in the lower lumbar spine and begins with fissures of the annulus, which may produce a disc herniation by time. The disc height is often severely reduced or finally lost, there is a lower heredity, the occurrence is rare before 30 years of age and both back pain and rhizopathy are frequent. Flexion forces of the spine is considered as a cause of this type of degeneration. As the annulus height is reduced, there will be incongruence and more strain to the facet joints, which can develop osteoarthrosis. With time the load will also proceed to the posterior elements of the vertebra, the laminae and spinal processes, ‘kissing spine’ or Mb Baastrup, an x-ray diagnosis well known in elderly people, but with few proven clinical connections yet [37]. Adams et al [15] believe that the two types of degeneration described above, are of different origins, but may finally progress in the same pathway, resulting in a complete disc failure, reduction.

These findings are, at least partially supported by other literature, showing the same radiologic distribution of Schmorls’ Noduli [38], others showing mainly genetical and some environmental evidence (lifting, bending and twisting at work), for the two different groups [39]. In a recent study by Li et al. [40], based on analysis of no less than 2,943 persons, genetical aspects, MRI-findings, descriptive and environmental risk factors for disc degeneration were studied. Also, this study supported the theory of two different etiologies of disc degeneration in the upper and lower lumbar spine, although overlapping, especially at the L3-4 level.

It is not possible to put an equal sign between degenerative findings in the spine and back problems in general. The pathoanatomical etiology to back problems has been extensively discussed in the scientific world for decades. The implication of such findings to the individual patient is though still not clear. Todays’ knowledge, as briefly described above, is though rapidly growing and is likely to continue to do so and produce answers by time.

4.5 Development of herniation

The definition of a disc herniation is now widely accepted; *localized disc material beyond the borders of the normal disc* [41]. It is usually a radiological definition, preferably with Magnetic Resonance Imaging (MRI) technique. The above described development of disc degeneration, ‘normal’ or not, is the prerequisite for the final development of a herniation. Purely ‘traumatic’ disc herniations, directly emerging from a ‘normal’ disc, without any signs of degeneration i.e. normal disc height and signal on MRI, without bulging, is extremely rare in the lumbar region [42, 43]. It may probably occur if accompanied by vertebral fractures, which usually is a result of only high energy trauma, at least in non-osteoporotic patients before upper middle-age. When degeneration is present (the overwhelming majority), the amount of trauma needed to provoke further degenerative events or progress, could be much less [44]. This is why patients

with lumbar disc herniation often refer their onset of pain to a fairly simple episode, like bending, lifting even light things or just stumbling [44].

4.6 Classifications

The degenerative process described above in Paragraph 4.4, is mostly a very slow process over many years or even decades. A sign of further progress is usually a more generally *bulging disc*. This process may also form a more locally bulging disc, *protrusion*, without penetrating the annulus fibrosus or posterior ligament and mostly posteriorly, or postero-laterally into the spinal canal. This totally predominant localization, is a result of anatomical conditions [45]. To this point the disc herniation is also classified as *'contained'* and consists of degenerated nucleus material. The disc material may continue and penetrate through the annulus and posterior ligament, but keep the continuity with the nucleus inside, *extrusion* or *perforation*, and it may finally loose the continuity and form a 'free' herniation of nucleus material in the spinal canal, *sequester*. The two latter types are usually called *'non-contained'*, with the perforation of the posterior border of the annulus and ligament, as the cut-point to contained herniation [46] (Figure 9).The described process, or parts of it, may have a much more rapid course in some patients. Especially perforation and/or sequestration, is often characterized of a very sudden onset of clinical symptoms. The immediate effect of the development of a herniation is pressure reduction inside the annulus and consequently acts like a 'security valve' [15]. Disc herniations are localized in 90%, equally to the two lowest segments (usually L4-5 and L5-S1), to 5% in the third segment from the bottom (usually L3-4) and in the other segments above in the remaining 5%.

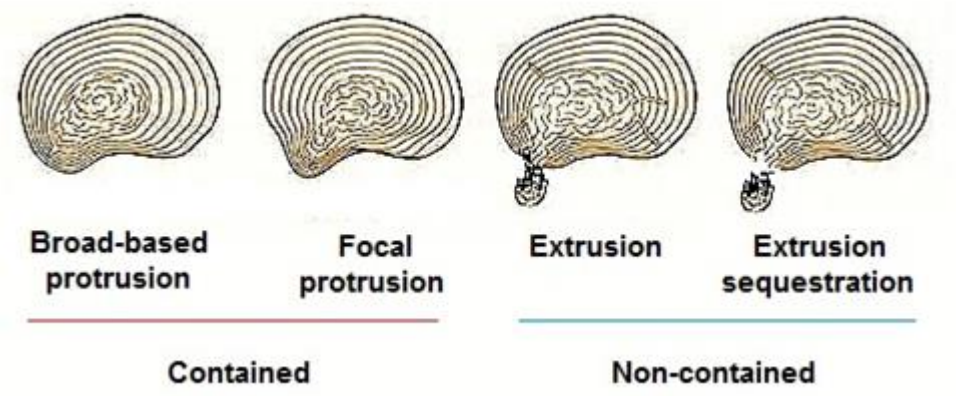


Figure 9. Classifications of disc herniation.

The above described classification, is primarily based on MRI, but have clinical implications. The history of different classification systems is contradictory and confusing, often based on pathoanatomical findings, not suitable for clinicians. One important advantage when using the definition of contained/non-contained, is that it seems to be of significance for the prognosis [47-49]. The non-contained herniation is generally vascularized from the epidural circulation and resorbed by time, usually predicting better outcome than for a contained herniation [50, 51]. The mainly used radiological classification from the American Society of Spine Radiologists (ASSR) [41, 52] is based on radiology and not clinical aspects but it is widely implemented, much because of its simple structure: *normal*, *broad-based protrusion*, *focal protrusion* and *extrusion* (Figure 9).

A very important piece of information, when classifying disc herniation, is its relationship to the neural elements (the nerve root, and the dural sac). In a recent review [53], the authors compared ten articles on root compression scoring systems. They found two being of good quality [54, 55]. The classification of Pfirrmann et al. is widely used today, describing nerve root compromise in four stages as *normal*, *contact*, *deviation* (of the root) and *compression*. (Figure 10).

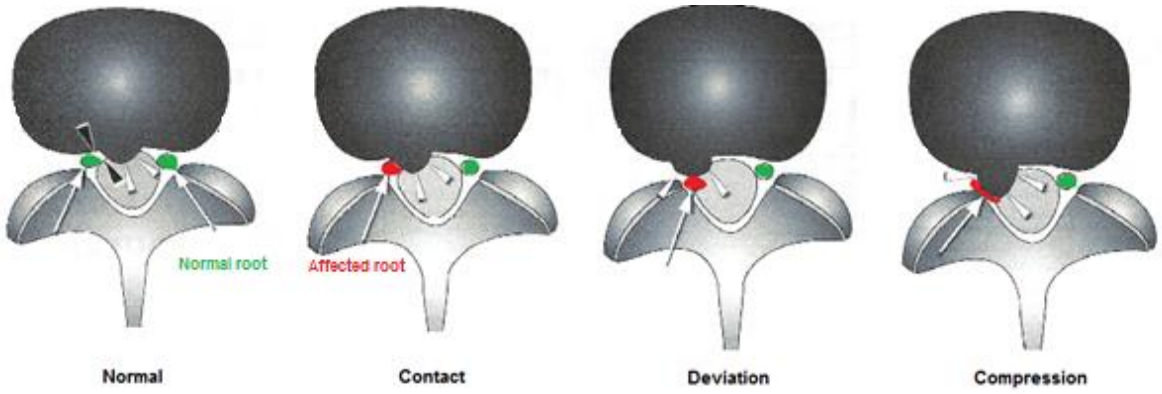


Figure 10. Classification of root compromise according to Pfirrman.

4.7 Epidemiology

As the 'anti-aging pill' is not yet invented and disc degeneration/herniation is mostly regarded as an expression of the aging spine, one could expect a higher prevalence of patients suffering from disc herniation in older age groups. However, the mean age of patients operated on due to lumbar disc herniation is world-wide between 40-45 years, inferring that disc degeneration is a phenomenon starting much earlier in life, already in childhood or adolescence [9]. It is probably the organ of the human body, that earliest shows signs of degeneration when other organs are still not fully matured. In childhood and adolescence degenerative findings are rare, but a recent German MRI-study of 103 children without spinal symptoms, with a mean age of 6,6 years, reveled 10.7% early signs of disc degeneration. The mean age of the adolescents with early signs of degeneration, was 12.5 years [56]. In another study from Korea on 102 asymptomatic subjects (aged 14-82, mean 46.3), the findings of nucleus degeneration at level L5-S1, increased from 0% amongst persons 14-19 years, to about 65% in subjects 60-69 years [57]. The conclusions of these studies are thus that signs of spinal degeneration by time is a very common finding even in asymptomatic persons.

The total *prevalence* of back pain and sciatica has been estimated to a point prevalence about 15-30% of *back pain* in adults and 60-70% in a lifetime [58-60].

The prevalence of *sciatic symptoms* is estimated to between 1,2% and 43%. Of those suffering from symptomatic disc herniation, about 90% will improve spontaneously by time [59]. Approximately 75% of these will recover within 3 months and 90% within a year.

In Sweden, the yearly number of surgically treated disc herniations, is about 2000, which gives an incidence of 20 operations per 100,000 inhabitants and year. This number has stayed almost the same since the mid-1950s, with an exception from the beginning of the 80s, when it started

rising until 1993, when it was 32. Thereafter it has gradually declined until 1999, again being around 20 and still is, with minor variations [61]. Interestingly the incidence of operations varies rather much around the world, from 10 per 100,000 in Great Britain to 70 in the USA [61]. This is probably not caused by a seven-times higher incidence of symptomatic disc herniations in the USA than in Great Britain, but an expression of different health care systems, access to surgery and different indications for surgery.

Lifetime incidence of having a symptomatic lumbar disc herniation, is a more uncertain calculation, but Frymoyer found between 13-40% 1992 [59] and Gugliotta et al 30%, in a recent paper [62].

The mean age of surgery for lumbar disc herniation is between 40-45 years, with a variation from about 10 to 90 years. Men are usually overrepresented in most reviews on the subject [61].

4.8 Asymptomatic - symptomatic

In a recent meta-analysis of MRI finding from 14 high quality studies, a total of 3,097 individuals, aged 15-50, were included [63]. Of these 38.6% were asymptomatic and 61.4% symptomatic, including back pain, sciatica and rhizopathy. When comparing different signs of degeneration; disc bulging, disc degeneration, disc herniation (both protrusions and extrusions), Modic type 1 changes and spondylolysis were all significantly associated with the symptomatic individuals.

In another recent meta-analysis signs of degeneration increased with age [64]. Disc signal changes increased from 17% among persons 20 years of age to 97% among persons 80 years of age. The authors concluded that degenerative changes per se are signs of age dependent degeneration, not necessarily associated with low back pain and must be 'interpreted in the context of the patient's clinical condition.'

4.9 Pain mechanisms

Where and how is pain in connection with a disc herniation produced? We have to differentiate between *back pain* and *leg pain,* and start with back pain.

4.9.1 Nociceptive vertebral innervation

The knowledge about the *vertebral innervation* anatomically was already in 1850 described by Hubert Luschka [65]. He showed how a small segmental nerve from each nerve root reentered throw the intervertebral foramen, into the spinal canal and innervated the posterior parts of annulus fibrosus and the posterior ligament. It was called 'recurrent nerve of Luschka', today the *sinuvertebral nerve.* These bilateral segmental nerves have later been shown to be highly overlapping, having connections both cranially and caudally and to the contralateral side. It has been shown that they also innervate the ventral dura, and most important, are capable of transmitting pain impulses [66]. The other parts of the vertebral segment have as well been demonstrated to be innervated e.g. the ventral annulus fibrosus and anterior ligament has its innervation from the autonomous nerve system, via the 'sympathetic trunk' [67]. A fact that probably is of importance for the emergence of 'referred pain' in the lumbar region (see p.4.9.2.6). The described overlapping of innervation is thought to be responsible for the often

diffuse localization of low back pain. Signs of innervation of the nucleus pulposus, have not been shown. Clinical pain provocation in humans, by injections of saline have been used to identify different pain producing structures in the back [68, 69]. The authors found annulus fibrosus to be the most likely pain producing structure. Low back pain in connection with a disc herniation may be produced by mechanical impact, annular tears or other damages, or a biochemical reaction (inflammation) in the annulus fibrosus and is etiologically *nociceptive*, pain is generated by stimulation of the pain receptors, 'nociceptors' in the tissue.

4.9.2 Rhizopathy

The second mechanism is the pain and symptoms produced by *impaction* from the herniation, directly *on the passing root(s).* The clinical signs of an impacted root are rather typical and thus usually corresponds well to the findings on MRI. This contrasts with the diffuse, unspecific low back pain, without pathognomonic findings on MRI.

The segmental structure of skin-innervation and the *dermatomal* distribution show a lot of overlapping and individual variation, but the distributions usually suffice to get a clinical diagnosis of the involved segment [70] (Figure 11). Not quite as well-known or used in clinical practice, is the segmental afference (input) from deeper structures, like muscles, forming *myotomes* and from bone, cartilaginous- and connective tissue, forming *sclerotomes.* The number of nociceptors (and thus neurons) in these structures are much lower than in the skin and pain from them are consequently much more indistinct and deeper. These patterns are not exactly following the dermatomes and their main importance in a clinical setting is often confusion, to the clinician [71].

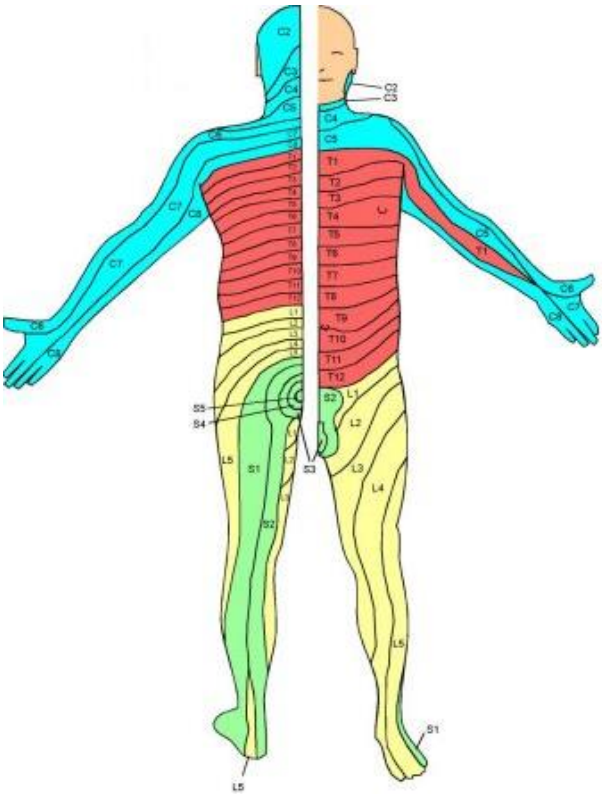


Figure 11. Dermatome map.

The most seen sciatic (rhizopathic) symptoms are from L5 and S1, or mixed. These involves even motoric changes in many cases. Solely motoric impaction, may also be seen, but more seldom. Impairment of the L5-innervated foot extension (drop foot), is a symptom rather frequently seen.

A special case is the feared *cauda equina syndrome**, where more or less of cauda equina is impacted. A complete case of maximal extent would imply loss of function in all neurons distally to approximately L2, motoric, sensory and autonomous.

***Cauda Equina** means *horse's tail* in Latin. It consists of all nerve fibrils leaving the distal medulla (conus), at L1-2, passing caudally in the dural sac before leaving the spinal canal, entering the root sleeve and forming the nerve roots, approx. L2 to coccygeal. If compressed, signs from all included fibrils may arise, including bladder, intestinal and genital functions.

The autonomous fibers are responsible for the function of the bladder, the intestine/rectum and genital organs. If the injury is cranially, it will imply Impaction of the last part om the medulla, the conus, which makes it to a mixed injury of peripheral/central neurons, with often worse prognosis [72]. Fortunately, most disc hernia induced cauda equina syndromes, are localized at the distal two segments and may involve function from L4 and distally [73] . Further, most cauda equina syndromes are not total, but partial, involving a 'random cluster' of peripheral/central neurons, with often worse prognosis [72]. Fortunately, most disc of all kinds of the neurons, most strongly affected by the often sequestered or perforated herniation. One-sided affection is not unusual [74]. prognosis in a review article by Chau et al [75]. In this review article the frequency of operated cauda equina syndromes were 2-6%. Affecting both sides, one can easily imaging there is a larger herniation, with often worse prognosis. The degree of completeness at the first appearance is the most important sign for the prognosis which, is dependent on the rapidity of onset, the pressure and the time of impaction, as in all neurological compression. There is no single point of time to do surgery before, that can imply better prognosis, instead, the quicker the better, is today the recommendation [76].

Compression of the neuron

When a disc herniation is *compressing* a root, the function will be disturbed, if the pressure is high enough [77, 78]. Oedema, inflammation and finally degeneration will take place. The way of compressive onset, slowly or rapidly, the amount of pressure needed and the duration of compression, have all been discussed as important factors in relation to the degree of neural damage that is seen. There are so far no 'cut-points' revealed concerning duration of onset, level of pressure or duration, of clinical importance. The biophysiological result is likely to be a complex mix of all three factors and is also depending on even more factors, e.g. inflammation [75, 76].

Inflammatory impaction of the neuron

The *inflammation* per se has also been found an important factor in the development of symptomatic impairment of the root [79-81]. Nucleus pulposus tissue has an acid pH and is shown to create inflammation when extruded into the spinal canal [80, 81]. This phenomenon is regarded as the mechanism behind the resorption of the tissue seen in such conditions (regression of herniation), but it may also initiate a reaction in the root, probably responsible for producing symptoms like pain [82].

The effects of compression and inflammation to the nerve root are complex but it seems as both can produce pain behavior in animal studies and that the mechanisms do interact, increasing the total effect if present at the same time [82, 83]. If compression is the only present way of impaction, it may not always result in pain, or other symptoms, explaining the vast number of asymptomatical individuals, discussed above [82]. One may regard an *asymptomatic* disc herniation as a necessary prerequisite to generate a *symptomatic* when or if an irritation causing inflammation adds its effects.

Results of impaction of the neuron

Impaction of the root can give two results. Either a *decrease or blockage* of impulses of the neurons resulting in paresis of motoric fibers, or hypoesthesia of sensible fibers. This is a result of *neuropraxia** or *axonotmesis** or even *neurotmesis**, depending of the degree of impaction

or injury [84]. The other reaction is an *increased signal activity* in the neuron. This is the neurophysiological explanation to pain, paresthesia and involuntary muscle reactions. The exact neurophysiological background to this 'state of irritation' is not fully known, but two models of impulse generating have been suggested; *ectopic impulse activity* [85] and *ephaptic impulse generation* [86, 87], the first meaning that an action potential – impulse, is *not* generated at the nociceptor, but from an 'irritable or injured' point somewhere along the neuron, the second meaning transmission of impulses *between* neurons, due to an injury of the myelin-sheath, surrounding the thicker fibers (A and B-fibers, Figure 11). Pain generated in

Fiber type	Nerve type	Myelin sheath	Modality
A-alfa	Aff + eff	X	Proprioception, motor
A-beta	Aff	X	Proprioception, superficial touch, pressure, vibration
A-gamma	Eff	X	Motor - proprioception
A-delta	Aff	X	Superficial pain, heavy pressure, cold
B	Aff +eff	X	Sympathetic functions
C	Aff		Deep pain, warmth, various autonomous functions

Figure 11. Classification of peripheral nerve fibers.

these ways are referred to as *neuropathic pain*, characterized by a process, due to an *injury* of the neuron(es). If affecting a *motor* neuron, it may produce corresponding effects, like generating fasciculations or muscle cramps [88]. A lumbar root consists of bundles of nerve fibrils (axons) which may emerge from all kinds of neurons, depending on which properties the affected root is equipped with. All lumbar roots (L1 – L5) and the first sacral (S1) contains both *efferent* fibers (conducting impulses outwards) and *afferent* fibers (conducting impulses inwards). The nerve fibrils are localized segmentally *within the dural sac*, with the lowest segments (S2-Coxxygeal) most dorsally and with the motor bundles anteromedially to the sensory. In the *root sleeve* the motoric bundles have reached a position directly ventral to the sensory [89, 90]. Further, the nerve roots do not have a perineurium, possibly making the roots more sensible to mechanical impaction [91].

The characteristics of a nerve fiber, depends on the thickness, varying from 0.1 to 20 mikrometer [92]. When being thicker than about 1 micrometer, an electrically isolating sheath covers the axon, the myelin sheath, gaining much higher conduction velocity. In the thinnest axon (C-fibers) impulses propagate with about 0.2 – 2 meter per second, but in the thicker (A- and B-fibers) with up to 120 meter per second. The highspeed A-fibers, are all used for life

* Classification of peripheral nerve injury, according to Seddon 1943.

Neuropraxia (Class I) is a temporary interruption of conduction without loss of axonal continuity.

Axonotmesis (Class II) involves loss of the relative continuity of the axon and its covering of myelin, but preservation of the connective tissue framework of the nerve (the encapsulating tissue, the epineurium and perineurium, are preserved).

Neurotmesis (Class III) is a total severance or disruption of the entire nerve fiber. A peripheral nerve fiber contains an axon (or long dendrite), myelin sheath (if existence), their Schwann cells, and the endoneurium. Neurotmesis may be partial or complete.

protecting purposes; motoric, balance, superficial protective pain or other modalities of sensibility (e.g. cold), being of importance for normal behavior [93]. B-fibers contain afferent sympathetic fibers and the thinnest C-fibers deep pain, warmth and wellbeing, not regarded as life protecting qualities, by evolution. The C-fiber mediated impulses do also have a close relation to autonomous system, giving reactions like tachycardia, nausea or dizziness. They constitute approximately 70% of a peripheral nerve (root).

4.9.3 Pain modifying mechanisms

Peripheral sensitization

When there is an injury somewhere, the body reacts to protect this area from further injury (by pain) and to induce a healing process. These reactions have been known for 2000 years, as the 'Celsus tetrad': calor (warmth), dolor (pain), tumor (swelling) and rubor (redness and hyperemia) [94]. Today we know this is the natural, primary, inflammatory reaction to an injury, not always superficial. It is mediated by the pain reaction from the afferents, via activation of their neurons, which start producing excitatory 'neuropeptides' (glutamate, substance P, CGRP), which by axonal flow is transported out in the periphery, where they are released in the injured area. At this point, they start the inflammatory reaction and lower the threshold for further pain. *Allodynia* (= usually not painful stimuli, creating pain or other unpleasant sensations) as well as *hyperalgesia* (=increased pain reaction) are seen. This reaction is today called *peripheral sensitization,* being a reaction of the peripheral neuron. It usually decreases after some days and is over within a week [92]. It is probably acting in the same way inside the spinal canal, an assumption supported by the discussion on inflammation above.

Central sensitization

There are also further important ways of reaction to tissue injury and pain. The sensitized peripheral neuron does have a sensitizing effect on the *central neuron* in the dorsal horn of the medulla as well. The excited central neuron starts an array of processes, that may result in *spreading of the pain* to neighboring segments, *allodynia*, *hyperalgesia* and *spontaneous pain* (during rest). This is also a totally normal reaction, likewise called *central sensitization,* in many aspects alike the peripheral, but spreading and spontaneous pain is specific for the central type of sensitization. With time and proper healing of the injury, the sensitization in most cases disappear, but in a minority of patients, it may be longstanding, even irreversible [92].

Referred pain

At the spinal level of the central neuron another important mechanism of pain can be elicited, *referred pain* [95]. This is a result of 'convergence' of afferent fibers from superficial bodily neurons, as well as from deeper, visceral fibers, into a lesser number of ascending central neurons. This may produce 'confusion' in the sensory cortex, on referring the impulses to the correct origin. Pain originated in deeper structures (visceras, vertebras) are experienced as coming from superficial areas (dermatomes). This is regarded a common etiology of radiating pain, in the absence of mechanical root impaction on MRI.

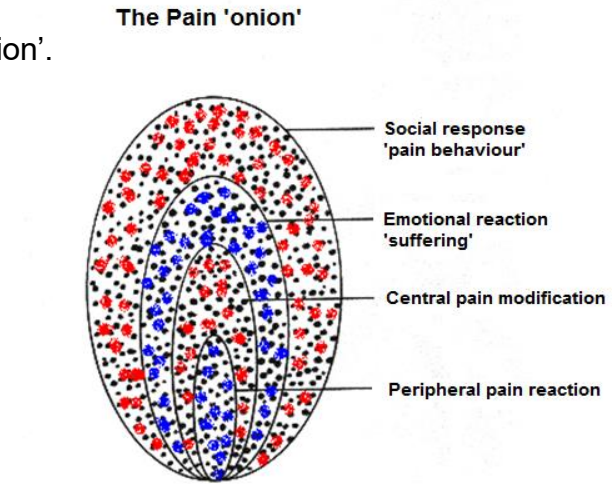
Central modifying mechanisms

The following paragraph is entirely based on Hansson [87] and Tullberg [92]. The final pathways of pain impulses up to the brain may, with the knowledge of today, not be described in terms of electrical wires from point A to B. The central nervous system has revealed an outstanding complexity and plasticity. It interacts with itself and the actual demands from the peripheral nervous system to optimize the function in every moment. On the medullar level, there are lots of different *interneurons* (connecting different parts of the medullary pathways), to facilitate or inhibit signal activity. Also, the brain has similar facilitating and inhibitory pathways to the medullary level, where they affect the ascending activity. Inhibitory dysfunction (*disinhibition*) of these controlling systems is believed to be at least a partial background to generalized pain, as in 'fibromyalgia'. It is often explained in terms like 'the pain brake doesn't work'. When the modulated pain impulses finally reach the brain, there are three main components of cerebral activity elicited (very simplified);

1. *A sensorial, discriminative component*, in the 'somatosensory cortex'. Intensity, localisition and duration is noted very rapidly, enabling immediate response in form of withdrawal or other protectionary mechanisms.
2. *An affective component* is created in the 'limbic system', with connection to emotions and memory, giving the pain reaction an 'emotional colour' of discomfort and suffering.
3. *A cognitive component* in the 'prefrontal and frontal cortex'. Here are the thoughts and consequences of the pain analyzed and the concious reaction formed.

A more extensive description of the processes involved in pain reactions, is far beyond the scope of this summary, but a general knowledge about how pain and pain reactions are created and the complexity of this item, helps the deeper understanding as well as daily clinical practice. It is both obvious and understandable that the pain reactions we meet in patients are much more than the primary stimulus, it is also a complex mix of personal and social characteristics and experiences. As a short 'summary' of the pain transmission and processing, the 'onion model' is helpful, where each shell represents a new quality in the perceptive pathway from injury to the complex personal reaction (Figure 12).

Figure 12. The 'Pain onion'.



Peripheral pain reaction ≠ pain behaviour.

4.10 Risk factors

Risk factors for developing symptomatic disc herniation have mostly been studied using disc degeneration as a marker. As we have seen above, this is not entirely correct in respect of the high rate of asymptomatic individuals. Another shortcoming is that some studies only judge MRI findings, without consideration to clinical symptoms and others only look at asymptomatic individuals [25, 96]. Until the turn of the millennium most efforts where focused on environmental and lifestyle factors, such as occupation, work load, leisure time activities, education, weight and smoking [17, 97]. Many of these factors showed some, but modest influence on the development of degeneration [98]. Studies on heredity and genetics, showed influence on disc degeneration. For example; 1995 a Finnish twin-study on 115 male twins, investigated with MRI, showed two patterns of hereditary influence, one in the upper lumbar region and one in the lower. In the upper part, the hereditary factor could explain 61% of the variability, to 34% in the lower part [24]. The results have been confirmed by others [25-27, 39] and strengthens the in Paragraph 4.4 described pathophysiological finding of two different types or degeneration by Adams [15]. Genetic variants with association to disc degeneration have been found, but the patterns are complex. Altogether, genetical factors seem to be of great importance for the development of disc degeneration and herniation, but a mix of other environmental and lifestyle factors, like physical load to the spine, are of importance for the expression of the genes [98].

4.11 Treatment options

The natural course of a lumbar disc herniation has a wide range from being asymptomatic, to emergency cases with total block of cauda equine function, needing urgent surgery. About 90% are healed with non-surgical management and in 75% < 3 months [59]. Conservative treatment will though not be discussed here.

There is a well-established, great consensus among spinal surgeons the world over, about indications for surgery of a lumbar disc herniation [99]. Thus;

1. Patients with cauda equine syndrome are regarded *emergency patients* surgically.
2. Patients with rapid onset of, or progressive paresis and *patients* with unendurable pain, as *subacute*.
3. Patients with persisting sciatica >2 months, without signs of improvement, are generally also regarded as *elective surgical candidates*.

The 3rd indication above, is probably most discussable; when, or if should a patient with lasting but endurable sciatica be offered surgery?

Weber [100] accomplished in 1970-71, the first randomized, prospective, controlled study on surgical and conservative treatment of patients with lumbar disc herniation. After excluding patients with more urgent surgical indications (1 and 2 above) and a group with less pain – without surgical indications, the remaining 126 patients were randomized to surgery or continued conservative treatment. 17 of the 66 patients in the conservative group did however prefer surgery during the first year, which confuses the statistics. The results however showed clearly better results for the surgical group at one year, but this was almost equalized at four years and at ten years the groups were equal. Therefore, showing a clear advantage for surgical

care up to four years, a considerable time with constant pain, this study has for decades been a cornerstone in the surgical judgement.

Others followed like *'The Maine Lumbar Spine Study',* a prospective cohort of 507 patients [101]. This study was mostly interpreted as supporting the study of Weber.

The *'Spine Patient Outcomes Research Trial', or 'SPORT'*. Of the originally 1,991 eligible patients, 501 meet the inclusion criteria in a randomized trial and 743, not accepting randomization, in an observational study [102]. Even this study supports the superiority of surgery. Thera are two more randomized studies on this item, a small Finnish study by *Österman* [103] (56 patients) and *Peul et al.* [104]. The latter randomized 283 patients with lumbar disc herniation, to 'early surgery' or 'prolonged conservative treatment', i.e. until the patient did not accept the pain situation and was operated on with delayed surgery. Österman showed slightly better surgical results up to six weeks. In Peul's study, surgery was better up to three months, but not thereafter. Notable is though that in the conservative group 31% were operated on < one year, with a mean of about three months, and 44% < two years.

The so fare latest study came in autumn 2016, when *Gugliotta et al.* presented a cohort study on 370 routinely treated patients, without randomization and with 20% non-surgically treated [62]. Even in this study surgery showed to be better up to three months, but not thereafter.

The conclusion of these 6 studies, seems to be that surgery relieves pain quicker than non-surgical treatments do. This may of course be of great importance to the individual patient but statistically the length of this period in favor of surgery has been reduced to three months from four years. Compared to non-surgically treated patients this period of improved quality of life is what motivates surgery. How well these studies are comparable with four decades between Weber and Gugliotta is though not easy to assess. Maybe there has been an indication shift in surgery over the years?

4.12 Surgical techniques

Surgery for lumbar disc herniation, has since the beginning, with Mixter and Barr 1932, been done with open surgical technique. Love, 1939, described it and with some modifications it is still the same [105]. In 1967 the operation-microscope was introduced by Yasargil [106]. Today, the numbers of open and microsurgical technic of LDH in Sweden are almost equal [107]. The open technique is though often facilitated by the use of loupes and direct illumination. Studies have not yet showed any advantages in the outcome, with either technique [108], the choice is up to the surgeons training and preferences.

Other techniques, like chemonucleolysis, and percutaneous nucleotomy of different kinds, have been tried and found not sufficient for general use [109, 110]. Epidural steroids shows lower efficacy than surgery, but may be a treatment option in some cases where surgery is not preferred [111]. Combined surgery, with fusion will not be discussed here.

4.13 Summary

At first, we must keep in mind that there is a definite number of patients where surgery has its obvious place; patients with cauda equine impaction and patients with intolerable pain. Also, patients with rapid onset or progression of substantial neurological dysfunction, will usually be

operated on quickly. There are no randomized studies on cauda equine impaction, but it would be regarded unethical not to operate such a patient, considering the time factor and risk for chronical impairment with delayed surgery [75]. The same argument is also raised concerning substantial neurological deficits. Patients with intolerable pain are usually not interested in waiting many days for an eventual spontaneous improvement and are operated non-electively [112].

We know fairly well that of all patients receiving surgery, approximately 75% will improve or recover. But is this enough to counterbalance the small, but unavoidable surgical risk and risk of complications, the risk (25%) of being in the 'wrong' group of outcomes and the societal costs for surgery, when a substantial part of the patients will improve quite satisfactorily by themselves, after some time of expectance?

Timing of surgery is very important and must be related to numerous factors of the patient involved. Initially, up to the 70s, surgery was usually delayed as long as possible, often by stressing the surgical risks. This 'long-waiting' regimen, did not only cause extended suffering for the patients, but may also have worsened the prognosis of improvement after surgery [113, 114].

From the 70s there was an increase in surgery, partially due to technical improvements, but probably also due to faster decisions on surgery [3, 115], maybe also lower demands of indications for surgery. One can presume this 'boom' of surgery created about 75% satisfied patients, but also many unsatisfied, some leading to a lot of 'failed back surgery' and chronic back problems [116]. Also, a number of complications in patients who otherwise probably would have been spontaneously improved by time. Under and after this period discussions and studies on indications for surgery, predictors for outcome and how to measure outcome, increased [102, 117-119], just to mention a few.

Most spinal surgeons today would probably wait at least 8 weeks before surgery, if not intractable pain [120]. But, what is intractable for one patient, may be endurable for another. Instead we individualize our judgement and try to find predictors that may help us in guiding the patient to a decision. If there are negative predictors we will probably recommend the patient to a longer expectancy, if none, we try to find out if the patient really understands what the surgery is about, including risks and an inferior outcome and what the patient really wants, before planning surgery. Thus, there is no exact limit of expectancy for these patients, it is always a discussion with each one, integrating all known facts in a holistic, individual judgement.

In this judgement, knowledge about predictors of outcome is most important, although satisfying multifactorial clinical models, will always suffer from some unmeasured bias.

When the Lumbar Disc Herniation Study (LDHS) was carried out, the primary aim was to search for clinically useful predictors that would help in this decision making. In this thesis, there is one article from LDHS on prediction, but several are planned. Swespine is, and will continue to be, an enormous source of epidemiological knowledge, if correctly used and with its shortcomings in mind. The other articles aimed a couple of relevant clinical questions, where our web searches, surprisingly enough, did not reveal very much on these items and finally the important question if results from Swespine are trustworthy.

4.14 Specific background in the papers

Study I

Children and adolescents are sparsely described in the literature. There are some retrospective studies of mostly small numbers of patients, varying follow-up time and different outcome measures [121-129]. The most commonly expressed treatment regimen, for patients younger than about 18 years, is expectation, based on the usually very good prognosis in children and a hesitation to use surgery in this group, in respect of later backlashes in form of reoperations in very young age. Several of the papers above have showed at least as good results for this age group, as for adults though. The number of reoperations vary widely from a 6% [126] to 20% in the long run [121]. The preoperative waiting time - expectancy, is thus longer for this group, than for adults [126, 130]. Is this a good treatment option in children with adequate symptom, MRI findings and sufficient expectancy?

Study II

Patients admitted to hospital via the emergency ward are often in a severe pain situation and a generally poor condition. Are their surgical results comparable to elective patients? A 'Pub Med' search on this item, showed some papers about 'cauda equine syndrome' [74, 76], but did not reveal one single article matching our question on patients admitted mainly because of severe pain and disability. There may be differences between the Swedish health care systems to other countries, but the patients are most likely the same. It seemed natural to look further on this issue. We aimed at including all non-elective patients, excluding the cauda equine syndromes, as this group has a worse prognosis.

Study III

Inflammation as part of the reaction seen around a disc herniation is an important part in the pathophysiology [82]. There are some studies implying that hsCRP, a routinely used measurement of inflammatory activity, may mirror the development of a disc herniation [131-133]. It could together with clinic and MRI, maybe contribute in the prediction of outcome.

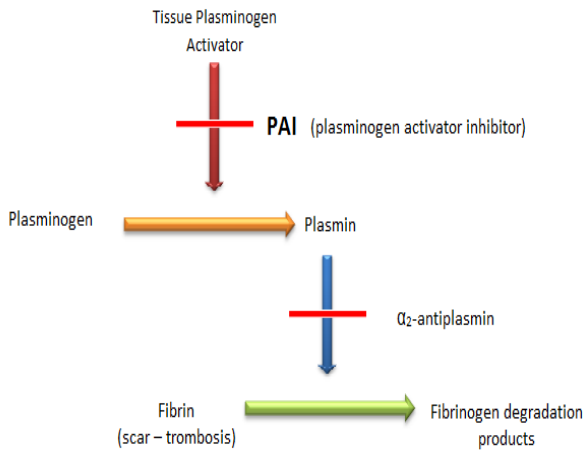


Figure 13. A very simplified scheme of Fibrinolysis.

When a wound heals, after surgery i.e., the normal reaction is primarily hemostasis by activation of platelets and the coagulative systems [134]. Fibrinogen adds and under the influence of thrombin starts the building of fibrin and polymerization of fibrin molecules, making a web like reinforcement in the beginning of scar formation. As with most other systems in the body, there is a regulating and counteracting system to modulate the scar formation (or thrombosis inside the vessels) [135, 136]. This is the fibrinolytic system. Very simplified, this acts by activating plasminogen to plasmin, a very

potent proteolytical enzyme, that immediately starts breaking down polymerized fibrin to its degradation products, thus reducing scars and thrombosis. The activation of plasminogen to plasmin, is meticulously regulated by other systems, in which the inhibitor of the plasminogen activator (Plasminogen Activator Inhibitor 1, PAI-1), has a central role [137]. The effect of this regulatory factor, is that it leads to more scar/thrombosis formation. (Figure 13).

It has been shown to be important in many areas of medicine, e.g. cardiology and cancer. In one study Dullerud et al [138], higher levels of PAI-1 predicted worse outcome after disc operation. For a long time, it has been a hypothesis that scar creation around the nerve root postoperatively could be a reason to persistent or recurrent pain after surgery. An association between high PAI-1 and worse outcome would thus support this theory.

Study IV

Data from national quality registers is a growing source of scientific works. The Nordic countries took a leading position in the world when introducing the 'personal identification number' during the 60s [139]. This action made linkage between different data sources possible with reliable accuracy. Large amounts of data are often gathered in a few years, by far more than even large multicenter studies use to recruit. Therefore, the *completeness* (the reported number of patients divided by the number of patients in the studied population), the preexisting database and the long-time perspective are the main advantages of these registers in outcome research [139].

On the other hand, the pre-collected data are not necessary the data of interest, may change by time and often lack information on confounders. Non-responders are a big problem in many registers that may bias the results. These are the main disadvantages.

The Swedish spine register (Swespine) has existed since 1993, primarily as a local register, but was during the last years of the 90s gradually introduced around the Swedish spine clinics [140]. The completeness is around 75% and the *coverage* (the number of clinics using Swespine divided by the number of clinics performing spine surgery) is around 90% [141]. It may be regarded as representing the absolute majority of spinal surgery in Sweden today, giving the register a high external validity. Of the drawbacks mentioned above, the fairly high number of non-responders is most often discussed, raising doubts for outcome data from Swespine. In study IV, we try a new way of addressing this item.

5 AIMS OF THE THESIS

Study I - Adolescents

To study outcome after surgery for lumbar disc herniation in patients aged 18 years and younger, in comparison to adults.

Study II - Non-Elective surgery

To study outcome after non-elective surgery for lumbar disc herniation, compared to elective surgery.

Study III - Inflammation and Fibrinolysis

To study outcome after surgery for lumbar disc herniation and the relation to inflammation and fibrinolytic activity.

Study IV - Validity of Swespine

To compare two prospective cohorts of patients operated on for lumbar disc herniation, Swespine and the Lumbar Disc Herniation Study (LDHS), with large differences in follow up rates, to evaluate the validity of Swespine.

6 PATIENTS AND METHODS

The four papers are based on *two cohorts of patients*. Flowchart on next pages.

6.1 Swespine

Patients

Swespine is the prospective quality register of spine surgery in Sweden and has since the start been developed continually. Today (autumn 2016) it contains over 110,000 spinal surgeries.

Preoperatively

'Opt-out' is used, which means that unless the patient actively declines participation, he or she is included. The surgeon registers diagnosis, type of surgical procedure, length of hospitalization and any complications occurring during the postoperative hospitalization. The patient is asked to fill in a questionnaire without the assistance of health care personnel, including data on anthropometrics, co-morbidities, smoking status, medication, work, sick leave and Patient Reported Outcome Measurements (PROMs) before surgery.

The following PROMs were used; back- and leg pain, measured from 0 (no pain) to 100 mm (maximum pain) on a 'Visual Analog Scale' (VAS) [142]; the 'Oswestry Disability Index' (ODI), a questionnaire for rating disability and function related to back problems [143, 144] giving a score from 0 (best) to 100 (worst); 'EuroQol 5-dimensions' (EQ-5D), a form measuring quality of life, translated to an index between -0.59 (worst) and 1.00 (best) [145] and 'Short Form 36' (SF-36) [146], another widely used quality of life instrument.

Follow-up

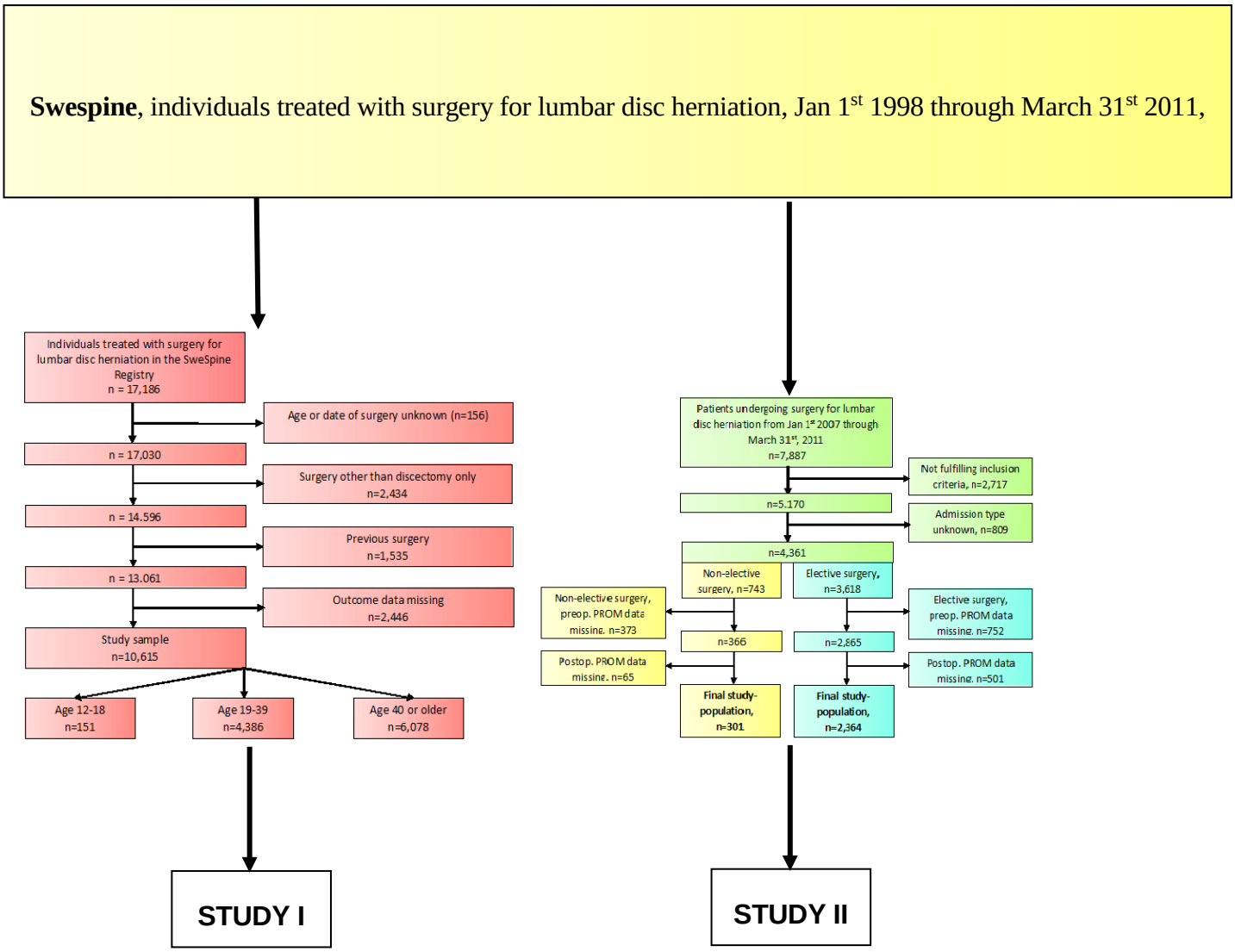
The patients are sent questionnaires 1, 2, 5 and 10 years postoperatively. They consist of questions on 'Satisfaction' and 'Global Assessment' (GA) of back- and leg pain [147], working status, sick leave or retirement and a couple of other questions, VAS back and leg pain, ODI, EQ-5D and SF-36. At the 1-year follow-up the patient is also asked whether any complications have occurred within 3 months after surgery, or if the patient has been reoperated. All questionnaires are mailed to the patient and answered without the assistance of personnel involved in the care. One reminder is sent.

6.2 Lumbar Disc Herniation Study

Patients

During the period, November 2004 through November 2010 a total of 455 consecutive patients were admitted for lumbar disc herniation surgery at Södersjukhuset, Stockholm, Sweden. Of these, 239 patients fulfilled the inclusion criteria beneath and were possible participators in a prospective, observational study. 59 patients were missed or not willing to participate and 3 were included incorrectly, thus 177 remained in the Lumbar Disc Herniation Study (LDHS). *Inclusion criteria* were; one-level lumbar disc herniation, radiculopathy with corresponding MRI finding, a duration of more than 2 months, or earlier if requiring hospitalization, a need for 25% or more of sick leave or similar disability and an age of 18 years or older.

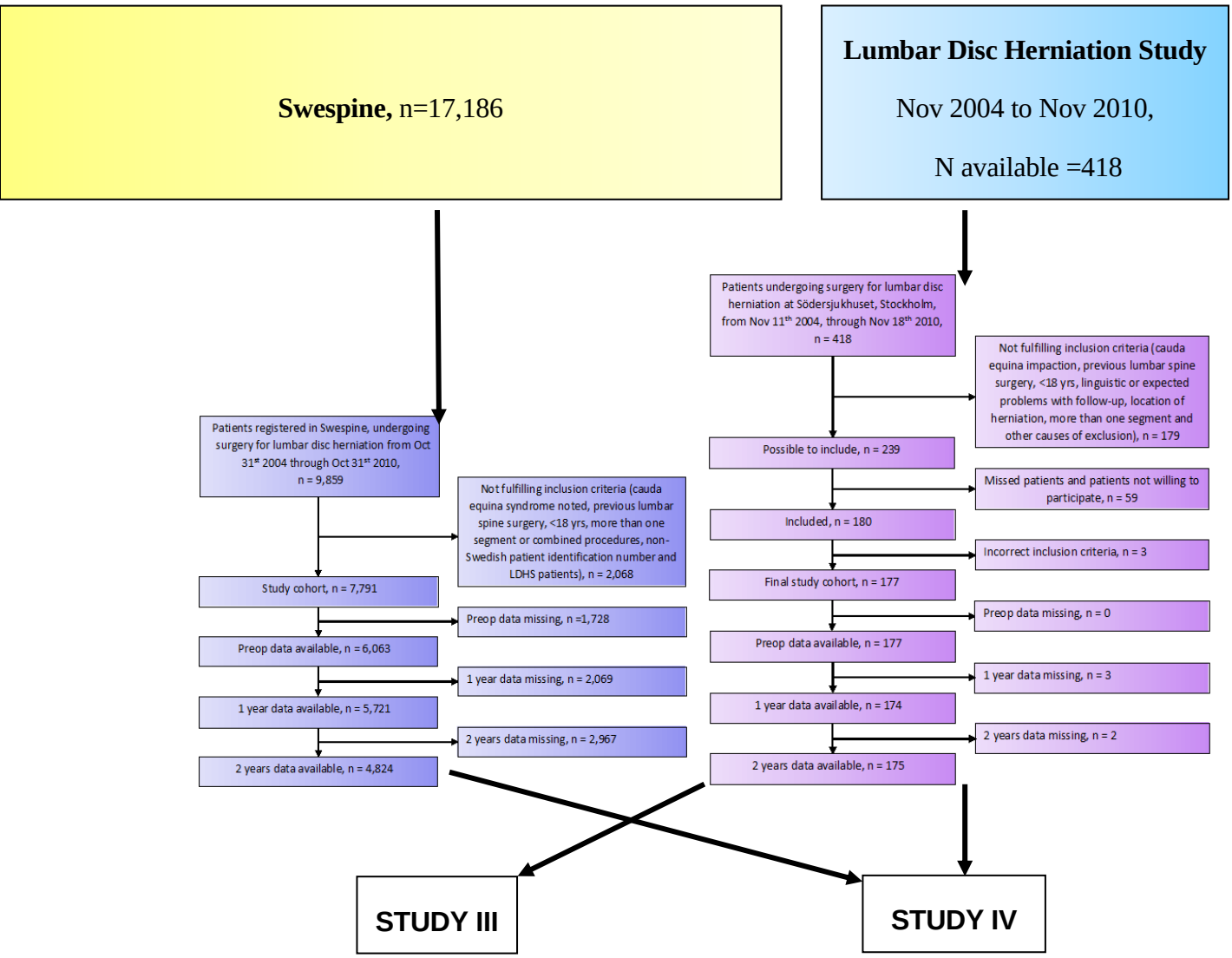
Flow chart of the total patient flow in the 4 studies:



Exclusion criteria were; previous lumbar spine surgery, cauda equina impaction requiring urgent surgery and conditions that could affect follow-up or outcome interpretation, such as more pronounced psychiatric illness, drug abuse or severe co-morbidity.

Preoperatively

These patients answered the same questionnaires as did the Swespine patients. They also completed some other questionnaires, went through a short clinical examination, blood analyses were taken (se beneath) and a special MR investigation were conducted, to be used in future studies.



Follow-up

The same self-assessment questionnaire as in Swespine, was administered at 6 weeks, 6, 12 and 24 months postoperatively. At 6 months, a follow-up MRI was done.

Laboratory analyses

Preoperatively, morning fasting blood samples were drawn, centrifugated, frozen and stored at –70° C, until the analyses of hsCRP, PAI-1, fibrinogen and D-dimer at the Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden.

6.3 Patients in each study and outcome measures

Study I

From Swespine, 10,615 patients operated from January 1998, through March 2011, were primarily included. The start date is when Swespine was introduced more extensively among the spine operating clinics in Sweden.
The patients were divided into three groups; aged 18 years or less (151 patients), aged 19–39 years (4,386 patients), and aged 40 years or older (6,078 patients). All above described PROMs, except SF-36, were used pre- and postoperatively, at 1 and 2 years. When 2 years-data was missing, 1 year-data was used.

Study II

From Swespine, 7,887 patients from January 2007 through March 2011, were primarily included. The start date depended on when the variable 'elective or non-elective surgery', was introduced in Swespine. After exclusions of patients with bilateral or medial location, cauda equine syndrome noted, earlier back surgery, more than one segment of surgery, unknown type of admission, preoperative missing data and non-responders at follow up, 2,665 patients remained, 301 non-elective and 2,364 elective patients. All above described PROMs were used pre- and postoperatively, at 1 and 2 years (except SF-36 and global assessment of back and leg pain). As in Study I, 1 year data were used, if 2 years-data were missing.

Study III

The 177 patients in the LDHS were included from November 2004 through October 2010.

Blood samples were analyzed preoperatively, for 'High sensitive C-reactive protein' (HsCRP), 'Plasminogen activator inhibitor 1' (PAI-1), fibrinogen and D-dimer. VAS for back and leg pain, ODI and EQ-5D were assessed pre-operatively and at 6 weeks, 6, 12 and 24 months post-operatively.

Study IV

Trying to use as similar inclusions and exclusions as possible in Swespine and LDHS, i.e. patients 18 years of age or older, with lumbar disc herniation and operated for the first time with a single-level discectomy between 2004 and 2010, we retrieved 7,791 patients from the 'Swespine' and 177 from the LDH Study. 'Patient reported outcome measurement' (PROMs), included VAS for back and leg pain, ODI, EQ-5D, 'patient's satisfaction' and 'global assessment' of outcome. Baseline variables accessible in Swespine, were compared to LDHS. Outcome at 1 and 2 years were also compared, as were complications and reoperations. Finally, a comparison of the cut-points for ODI and VAS leg pain, for being satisfied with the operation or uncertain/not satisfied, were done in the two study groups.

6.4 Outcome measures – general aspects

All used outcome variables in this thesis are those used in Swespine. They were originally chosen by Swespine as they are used, well known and validated worldwide [148] and are understood by researchers all over the world, an extremely important aspect of communicating

scientific works. All variables are Patient Reported Outcome Measures (PROMs), which today are generally accepted and recommended outcome variables in spinal research [149].

There are two types of outcome variables. In the first, the patient estimates the *actual degree of symptoms* (e.g. pain, disability and quality of life), using either a scale or answering a questionnaire corresponding to the intended area of interest. The questionnaire most frequently consist of multiple-choice questions, from which a value can be calculated. The values from different points of time, can then be used to calculate a result. [147].

In the second type of variable, the patient estimates the *change of a symptom over time*, e.g. before and after surgery. Again, by multiple-choice questions such as; free of symptom, much better, better, unchanged or worse. This kind of variable is referred to as *Global Assessment* measurement (GA). They are generally considered being the 'golden standard' in outcome research and evaluation of other outcome variables. They may be affected of 'recall bias' e.g. the patient does not remember the primary situation, or the memory has changed due to affective circumstances [147].

The PROMs used are shortly described in Paragraph 6.1 ; Back- and leg pain 'Visual Analog Scale' (VAS) [142], 'Oswestry Disability Index' (ODI) [143, 144], 'EuroQol 5-Dimensions' (EQ-5D) [145] and 'Short Form 36' (SF-36) [146]. As global assessments, questions on 'Satisfaction' and GA of back- and leg pain are used [147]. The Satisfaction question is formulated; 'Are you satisfied with the result of the surgery?' The GA of back (leg) pain questions, are formulated 'How is your back (leg) pain today, when compared to before surgery?'

The choice of the first four variables are according to generally accepted recommendations on outcome measurement. Different aspects of outcome should be measured; pain, disability and quality of life [149].

Concerning the variables on the scale (VAS pain, ODI, EQ-5D, and SF-36) the grades that are of importance to the patient 'Minimal Clinical Important Difference' (MCID), has been widely discussed [119]. This is an important measure in all studies, especially in those where the number of patients is high (register-studies), as this will give statistical significance to many analysis, despite that the clinical difference is very low and not at all interesting (lower than MCID value).

Finally, *complications* and *reoperations* are calculated in the different studies, as being important measures of surgical disadvantages.

6.5 Statistics

Statistics are used to describe data and relations between groups in respect of chance. In the here presented works, we have strived to use statistics clearly sufficient for the aimed purpose, but also as comprehensible as possible, to make the presentation more accessible.

Descriptive data on nominal level (not ordered categories) or ordinal level (ordered categories), is analyzed with *Chi-square test*. The analysis of numerical data is depending on distribution of the variable. When normally distributed (equal variances), the *Students t-test* were used, if not, the *Welch-Satterwaite's t-test*. When calculating with covariables, *Analysis of Covariance (ANCOVA),* or *linear regression* was used for continuous, dependent variables and if

dichotomized (divided into 2 values), *logistic regression*. When deciding sensibility and sensitivity of ODI and VAS leg pain, in respect of 'Satisfaction' in both cohorts, *Receiver Operating Characteristics (ROC) curves* were used. If repeated calculations were done on the same group, i.e. over time, *Wilcoxon's signed rank test* was used.

All analyses were done with the 'Statistical Package for Social Sciences' (SPSS) versions 22-23 (IBM).

6.6 Ethics

All patients available for registering in Swespine, are receiving their care within the ordinary health care system. 'Opt-out' is used but all patients are informed about Swespine and participation is of course voluntary. Written consent is yet not necessary in quality registers in Sweden. Study I, II and IV have an approval from the Ethical Review Board in Stockholm 2012/206-31/1. The LDH Study is as described more extensive, with special MRI and blood sampling. Written information and signed consent was mandatory. There is an approval for all parts of the study from the Ethics Committee at the Karolinska University Hospital Huddinge 410/1998.

7 RESULTS

Study I

86% of the adolescents were satisfied, compared to 78% in the younger adult and 76% in the older adult group. The global assessment of leg pain was significantly decreased in 87% of the adolescents, 78% of the younger adults and 71% of the older adults. Corresponding figures for back pain was 88%, 73% and 70%, respectively. All group comparisons were highly significant. The frequency of reoperations between the groups did not differ significantly.

Compared to preoperative values, all groups experienced significant post-operative improvement of VAS leg pain, VAS back pain, ODI and EQ-5D and adjustments did not change the outcome results substantially (Table 1 and 2).

The follow-up consisted of 78% two years results and 22% from year one, making totally 81% follow-up.

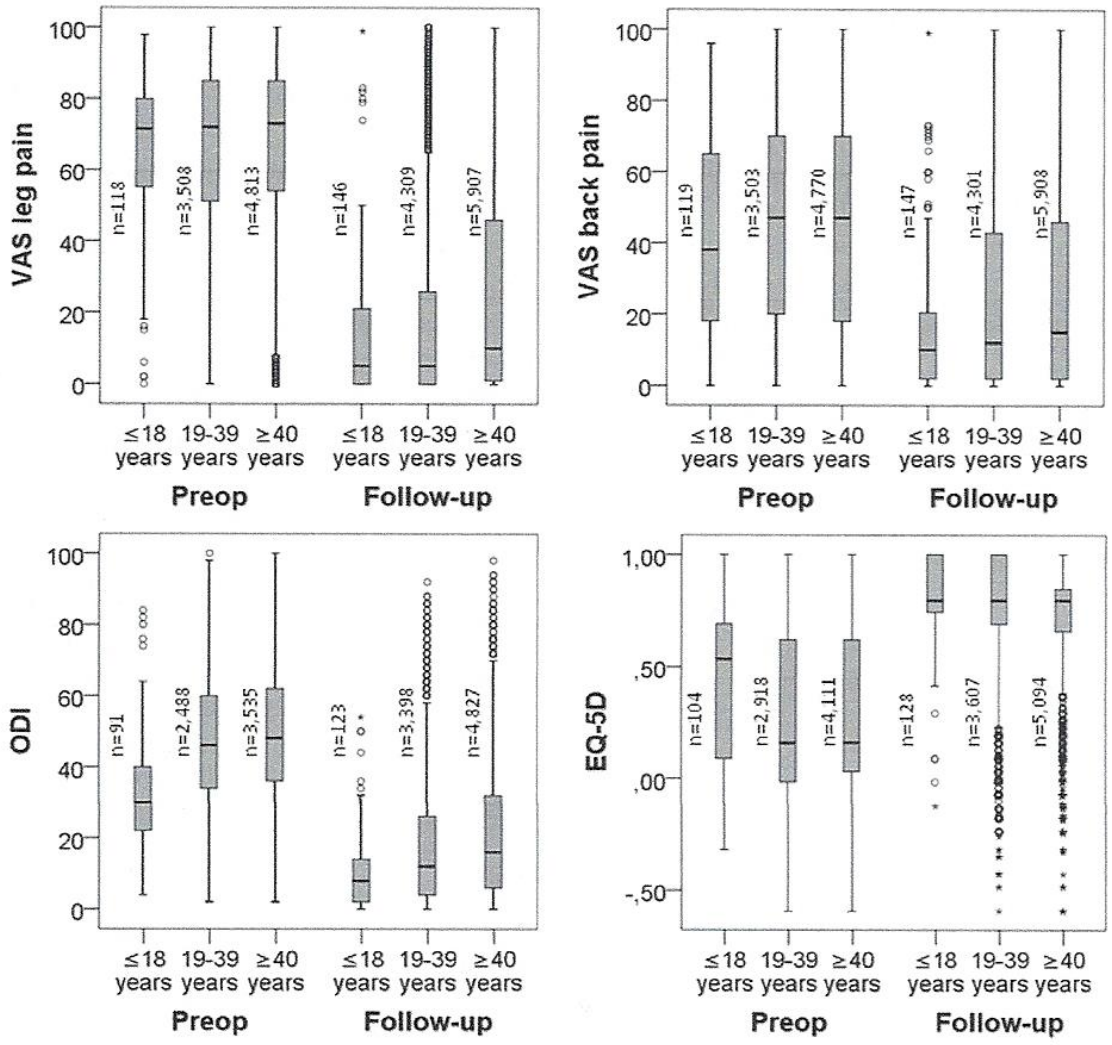


Table 1. Pre- and postoperative PROMs in study I.

Table 2
Satisfaction and global assessment 1 to 2 years after surgery

Outcome	Age ≤18 y (n=151)	Age 19–39 y (n=4,386)	Age ≥40 y (n=6,078)	Unadjusted p value	Adjusted p value
Satisfaction					
Satisfied	128 (86%)	3,362 (78%)	4,479 (76%)		
Uncertain/dissatisfied	21 (14%)	925 (22%)	1,436 (24%)	<.001	.043
Global assessment leg pain*					
Pain free/much better	130 (87%)	3,337 (78%)	4,191 (71%)		
Somewhat better/unchanged/worse	20 (13%)	951 (22%)	1,691 (29%)	<.001	<.001
Global assessment back pain†					
Pain free/much better	120 (88%)	3,025 (73%)	3,959 (70%)		
Somewhat better/unchanged/worse	17 (12%)	1,108 (27%)	1,714 (30%)	<.001	<.001

Note: Data are given as n (%). Unadjusted p values are given for the Pearson chi-square test and adjusted p values for analysis of covariance after adjustment for sex, smoking, type of disc herniation, and duration of preoperative leg and back pain for the differences between the three groups. Numbers do not always correspond to group numbers because of missing data.

* There were 0 adolescents, 43 younger adults, and 94 older adults who did not experience leg pain before surgery.

† There were 12 adolescents, 189 younger adults, and 312 older adults who did not have back pain before surgery.

Table 2. Global assessment study I.

Study II

At baseline, the non-elective group showed more pain, lower function and quality of live than did the elective group. In the non-elective and the elective groups, the mean (SD) figures were respectively; VAS leg pain 81 (22) and 65 (24), VAS back pain 51 (33) and 44 (28), ODI 66 (20) and 45 (17) and EQ-5D 0.024 (0.35) and 0.31 (0.33), respectively (p for all <0.001).

Postoperatively, VAS leg pain was 23 (28) in the non-elective group and 20 (26) in the elective group (p=0.019). Corresponding figures were for VAS back pain 25 (27) and 24 (27) (p=0.69), ODI 19 (17) and 17 (17) (p=0.052) and for EQ-5D 0.70 (0.28) and 0.73 (0.29) (p=0.73), all adjusted figures. Patient satisfaction did not differ between the groups (p=0.78). The number of measured complications in the two groups were the same, but there was a two-fold increase of reoperations of recurrent disc herniation among the non- elective patients (p=0.012). At follow up 79% of the answers were from two years and 21% from one year (Tabell 3).

Table 2 Pre- and postoperative, 1–2-year absolute values, for the patient reported outcome measures (VAS leg pain, VAS back pain, ODI, EQ-5D) in the non-elective and the elective group

	Non-elective (n = 301)	Elective (n = 2364)	p value[a]	p value[b]	p value[c]
Preop.					
VAS leg pain	81 (22)	65 (24)	<0.001	<0.001	–
VAS back pain	51 (33)	44 (28)	<0.001	<0.001	–
ODI	66 (20)	45 (17)	<0.001	<0.001	–
EQ-5D	0.02 (0.35)	0.31 (0.33)	<0.001	<0.001	–
Post-op. 1–2 years					
VAS leg pain	23 (28)	20 (26)	0.09	0.026	0.19
VAS back pain	25 (27)	24 (27)	0.44	0.29	0.69
ODI	19 (17)	17 (17)	0.08	0.043	0.052
EQ-5D	0.70 (0.28)	0.73 (0.29)	0.046	0.033	0.73

Data are shown as mean (SD). *P* values are shown for analysis of covariance (ANCOVA)

[a] Non-adjusted *p* value

[b] Adjustment for preoperative BMI, co-morbidities, and duration of preoperative leg and back pain

[c] Adjustment for preoperative BMI, co-morbidities, duration of preoperative leg and back pain, and baseline value of the dependent variable

Tabell 3. Pre- and postop PROMs Study II.

Study III

There was a high response rate in the Lumbar Disc Herniation study. At 6 weeks, 6, 12 and 24 months, 174, 172, 173 and 175, out of the initially 177 patients, responded to the questionnaire respectively. The associations between PAI-1 and outcome seemed to be most prominent at the 6 and 12-month follow-up. When being in the upper half of PAI-1, the OR (CI) for being in the worst quartile of VAS back pain 12 months postoperatively was 3.33 (1.56-7.10). The corresponding OR for VAS leg pain was 2.46 (1.18-5.10), for ODI 2.83 (1.35-5.94) and for EQ-5D 2.73 (1.30-5.75). The OR for hsCRP was 2.10 (1.03-4.29) for being in the worst quartile of VAS back pain. In our study, 75% of patients had a duration of *back* pain longer than three months and 81% of *leg* pain. Dichotomizing duration of *back* pain at three months, showed an almost doubled mean in the group with shorter duration 3.70, than the other group, 1.87. For *leg* pain, corresponding figures are 3.92 and 1.95. The differences were not significant though, p=0.59 and p=0.11 and respectively. Fibrinogen or D-dimer was not associated with any outcome variable.

In summary, high PAI-1, a marker of decreased fibrinolysis, was fairly consistently associated with poor outcome at 6 and 12 months, while hsCRP, fibrinogen and D-dimer were independent of outcome at any point of time (Table 4).

Table 2 Odds ratio (95 % confidence interval) of being in the worst quartile of VAS leg pain, back pain, ODI, or EQ-5D when in the upper half of PAI-1 vs. the lower half of PAI-1 at the different points of outcome

	Preoperative		6 Weeks postop		6 Months postop		12 Months postop		24 Months postop	
	U	A	U	A	U	A	U	A	U	A
VAS back pain	1.08 (0.54–2.19)	1.16 (0.52–2.63)	1.72 (0.84–3.53)	1.23 (0.52–2.89)	1.72 (0.84–3.53)	2.02 (0.85–4.78)	**3.33 (1.56–7.10)**	**4.78 (1.88–12.15)**	**2.28 (1.11–4.70)**	2.08 (0.88–4.93)
VAS leg pain	0.52 (0.25–1.07)	**0.39 (0.16–0.91)**	**1.08 (1.54–2.19)**	1.05 (0.45–2.49)	**2.70 (1.10–6.61)**	**4.25 (1.50–12.07)**	**2.46 (1.18–5.10)**	2.15 (0.91–5.06)	1.75 (0.86–3.55)	1.40 (0.60–3.27)
ODI	0.67 (0.21–2.28)	0.57 (0.15–2.16)	1.64 (0.86–3.12)	1.65 (0.77–3.54)	**3.82 (1.33–10.98)**	**4.72 (1.44–15.46)**	**2.83 (1.35–5.94)**	**3.36 (1.37–8.28)**	1.96 (0.91–4.00)	1.74 (0.73–4.16)
EQ-5D	1.02 (0.51–2.02)	0.76 (0.34–1.70)	1.92 (0.94–3.94)	1.65 (0.71–3.87)	**2.50 (1.20–5.22)**	**3.42 (1.41–8.29)**	**2.73 (1.30–5.75)**	**2.72 (1.12–6.57)**	**2.62 (1.26–5.44)**	**2.77 (1.14–6.71)**

Adjustments have been done for sex (female vs. male), BMI, smoking status (current smoker vs. non-smoker), and groups of analysis. Significant associations are shown in bold
U Unadjusted, *A* Adjusted

Table 4. PAI-1 and outcome study III.

Study IV

When comparing the two cohorts at baseline there were only minor differences in the PROMS, all well within reported 'minimal clinical important differences' (MCIDs). The mean follow-up rates at 1 and 2 years were 73% and 62% (Swespine), compared to 98% and 99% (LDHS). The mean *improvement* of outcome was highly significant in both groups, compared to baseline values, but not *between* the groups after surgery and the *absolute*, postoperative values very similar. All outcomes at 1 and 2 years were similar in both groups and differences well within the reported MCIDs (Table 5). Except for postoperative infections, which were doubled in the LDHS group, complications and reoperations showed almost equal values. Sensibility and sensitivity for ODI and VAS leg at 1 year, for satisfaction, were much alike in both cohorts. Non-responders, compared to responders at follow up 1 and 2 years, showed to be slightly younger, of male sex, unemployed, smokers and had heavier physical work strain.

Table 5. Postoperative results at 1 and 2 years, shown as the *mean difference* from pre- to postoperative values (SD) and corresponding P-value. Significant values in bold types. For the questions on 'Satisfaction' and 'Global assessment' (GA), the proportion of *satisfied* and *pain free* or *much better* respectively, is shown. Statistical analysis is conducted with ANCOVA for continuous variables and logistic regression for categorical variables. The missing percentage answers in each calculation is shown. All values are unadjusted. [a] Scale 0 – 100, 0 = no pain (VAS) or disability (ODI); [b] Scale -0.59 – 1.00, lower = worse.

	1 year results				
	Swespine		LDH study		P-value
		Missing %		Missing %	
VAS back pain [a]	21 (32)	43	27 (32)	2	0.012
VAS leg pain [a]	47 (33)	43	46 (32)	2	0.69
ODI [a]	30 (22)	43	29 (25)	2	0.41
EQ-5D [b]	0.46 (0.41)	43	0.45 (0.46)	3	0.63
Satisfied	78%	28	78%	3	0.96
GA back pain	72%	27	73%	12	0.76
GA leg pain	76%	27	73%	12	0.30
	2 years results				
VAS back pain [a]	21 (33)	52	28 (31)	2	0.011
VAS leg pain [a]	47 (34)	51	44 (32)	2	0.41
ODI [a]	31 (22)	52	29 (25)	1	0.37
EQ-5D [b]	0.47 (0.40)	51	0.42 (0.47)	2	0.13
Satisfied	80%	39	76%	4	0.31
GA back pain	74%	43	77%	23	0.45
GA leg pain	77%	40	71%	17	0.16

8 DISCUSSION

Study I

Other authors have assessed the outcome after disc surgery in adolescents in retrospective studies and fond a better outcome after one year than for adults [121, 128, 129]. The adolescent group was statistically better for ODI and EQ-5D at baseline, but clinically far from being of any importance [118, 119, 150, 151]. Other baseline characteristics of the three groups differed in respect of smoking, as there were only about 1/3 as many smokers in the youngest group, compared to the oldest. This could predict a better outcome for the younger group [152]. Pain duration, especially leg pain, showed 8% higher frequency in the youngest group for pain more than three months, compared to the oldest group, a factor usually regarded as a negative predictor [114]. Altogether this could predict a better outcome for the adolescent group, which also is the result, but even after adjustment for gender, smoking, duration of pain preoperatively and type of herniation, the results were similar.

Non-responders were compared to the total group preoperatively and were found to be slightly younger, more were smokers and they had a longer preoperative duration of pain. Adjustments for these variables between the *responding* groups, did not impact the outcome appreciably, as stated above. Thus, the much smaller *non-responding* groups are not likely to do so either. A study on register patients from Norway, show that 22% of lost patients to follow up did not impact the result [153]. The mix of outcome data from one and two years is a limitation, but today most studies show one year data as short time outcome and great similarity in data from one and two years [140].

In summary, this study shows that surgical treatment of lumbar disc herniation in adolescent patients (less than, or 18 years) is at least as successful as it is for older patients, in the short perspective. Studies on outcome in a longer perspective are still necessary, to evaluate the risk of later deterioration, due to surgery induced degeneration.

Study II

Patients with sciatica are rather frequent at emergency wards in Sweden and probably elsewhere. The unbearable intensity of pain forces patients to seek immediate help and many are admitted to hospital care for further pain control. If no signs of ‘cauda equina’ impaction is obvious, the attitude to surgery is often initially expectant, as quite a few will improve in some days and could be discharged. The remaining patients are usually operated on as soon as possible, to shorten their intolerable pain. Compared to the elective group, still managing their life situation, with sick-leave and pain-killers at home preoperatively, the corresponding figures showed highly significant *statistical* differences to the non-elective group. The *clinical* difference, measured with ‘minimal clinical important difference’ (MCID), was well over the proposed value for ODI, around the proposed values for EQ-5D and VAS leg pain and clearly lower for VAS back pain [147, 154, 155]. These circumstances most probably explain other preoperative group differences, such as pain duration and hospitalization time.

The higher initial pain levels of the non-elective group would be expected to imply a worse outcome [156], maybe a little modified by the shorter period of pain preoperatively [157], in

this group. The outcome at 1 and 2 years was however surprisingly equal in all measured aspects. Almost no statistical significant differences and all clinical far lower than MCIDs. This means that the non-elective group improved clearly more than did the elective patients. Complications were at the same level, except for the frequency of reoperations within 2 years, which was twice as high in the non-elective group. The frequency of reoperations (4-8%) is though at level with other reports, 5-10% [158-160]. Theories on differences in type of herniation (contained or non-contained) could be considered [49], but is not noted in Swespine and thus impossible to verify.

There are several limitations in this study, as no definitions of non-elective/elective in Swespine, the use of mixed 1 and 2 years' follow-up, 'cauda equina' patients not being noted in Swespine and the unmeasured confounding in register studies. The maybe most important limitation, is the mix of follow up times, but according to Strömqvist [140], this is not a problem.

A conclusion of this study is that the nerve root has a great capacity of healing and returning to (almost) normal function again, after proper mechanical decompression, despite probably serious affection from the herniation. This is provided that the affection has not damaged the neural function incurably [161-163].

Study III

Inflammation as a part of the pain generating process in disc herniation and degeneration has been recognized for 2-3 decades [80, 164]. Local signs of this inflammatory process have been found in the epidural space [165] and cerebrospinal fluid [79]. Findings of higher levels of CRP in peripheral blood samples, have been done [131-133]. The possibility of using a simple test, to decide the level of actual inflammation, could be of great interest, both for deciding the optimal treatment and eventually for prediction of outcome. Our study did not reveal such a clear association, except for a borderline value at one year for VAS back pain and hsCRP. The methods of analysis used were routine methods of high sensitivity and reliability. Stürmer et al [132] indicate an association with more acute *sciatic* pain (shorter than two months) but not with chronic low *back* pain. It is difficult to compare to our group, as most of the LDHS patients had *both* back and leg pain. The means in the short duration group, are slightly above the normal value (<3.0). This may eventually support Stürmer's findings and would possibly be significant if the time scale for duration had been more exact.

'Scar formation' is a phenomenon that follows after all surgical interventions and also after long-standing inflammation [135, 166]. It is a normal phenomenon in the healing process after surgery or trauma. It has however been proposed that in some cases, scarring may be responsible for, or contribute to persisting or recurrent pain after disc surgery when no mechanical impaction can be visualized on a postoperative MRI. Hemostasis is a very complex mechanism with interactions involving many delicate systems in the balance between bleeding and thrombosis. In fibrinolysis, the process responsible for resolving thrombosis and remodeling of extensive fibrosis, a major regulator is 'Plasminogen Activator Inhibitor 1' (PAI-1) [137, 167, 168]. Impaired function of fibrinolysis was already in the 80s suggested as a cause of chronic back pain, with or without surgery [164, 169]. PAI-1 is a very useful marker of fibrinolysis, but is also involved in many other processes like

arteriosclerosis, cancer and inflammation. One study by Haaland et al 1992 showed an association between higher PAI-1 and poor outcome after disc surgery [170]. Others have not been able to reproduce this result [171], but this study was fairly small, 40 patients including controls. Our study show clear associations between high PAI-1 and poor results of all 4 outcome variables, with a peek at one year, meaning that patients with worse outcome showed signs of impaired fibrinolysis (Table 4). This may result in more fibrosis and the fibrosis may cause more pain and dysfunction. Our hypothesis may be strengthened by these findings, but definitely not proven. The mechanism behind such an association is still unknown.

In a recent review article [135] *inflammation and angiogenesis* are believed to interact in scar formation. An initially excessive angiogenesis may result in cellular death in the deficient capillaries, causing a lot of fibrosis and, as a paradox, an end result with a fibrotic scar and insufficient blood supply, leading to even more fibrosis. Fibrinolysis is not the point in this article, but an insufficiency of this system would quite likely have a further negative impact on the situation. If this rather trustworthy hypothesis will be shown correct, the negative effects of perineural fibrosis and scar formation would, at least partly, be a result of deteriorated blood supply. Future research on this item, including the role of fibrinolysis, is strongly recommended, if better to understand the cellular processes behind failed lumbar disc surgery.

Study IV

Our way of facing the problem with non-responders is to compare data from a prospective cohort study (LDHS) with Swespine on surgically treated lumbar disc herniations. This study is indeed much smaller, but has a very high rate of follow-up, giving high internal validity. Comparing base line characteristics, outcome at 1 and 2 years and cut-of values of ODI and VAS leg, for being satisfied with the result, in both cohorts, would give valuable information about the comparability of Swespine and LDHS.

The results of this comparison show that the cohorts are surprisingly alike. There are small differences at baseline such as age, comorbidities, retirement and disability pension and the patient's belief in returning to work. The LDHS cohort was 3 years younger in mean, the maximum age is 92 (Swespine) and 74 (LDHS) years. In Swespine, there is a decline in persons born during the forties and a peek during the fifties. This decline in the number of persons around 60 years is clearly more prominent in the LDHS, resulting in fewer elderly persons. The reason for this is unknown. This circumstance, and the difference in maximum age, may probably explain some of the difference in the mean of 'Age', as well as in the 'Comorbidity', the 'Retirement' variables, and 'the patient's belief in returning to work', as these variables all seem to correlate with age. When calculating the outcome, we also adjusted for these differences, with only minor effects. Thus, we believe these cohorts are comparable regarding baseline characteristics and outcome, for the here described purpose.

Another result is that at least concerning lumbar disc surgery, the *non-responders* in Swespine, cannot reasonably differ substantially in their results from the responders. Why?

- At baseline Swespine and LDHS are fairly equal.
- At follow-up the responding group in Swespine and LDHS is very similar and adjustments do not change this similarity.
- If the non-responders would have been substantially different from the responders concerning results, this would have led to a corresponding difference among the responders, which is not the case.

This can further imply the conclusion that missing cases in Swespine are mostly lost at random, strengthening the results of Swespine, though showing a considerable number of non-responders at follow up.

General aspects

Limitations in these studies are mainly attributable to the study populations. In study I and II, this is Swespine, with its inevitable problem of non-responders at follow up, which is discussed above. In study III, it is LDHS, a much smaller cohort, with a very high rate of follow-up, giving the study high internal validity, but how representative is this material compared to another population, how generalizable is it? This question is partly answered in study IV, where the two cohorts were found to be much alike. A fact that not only gives a certain internal validity to Swespine, but also some external to LDHS. There could have been a control group of non-operated patients in study III, regarding the levels of hsCRP and PAI-1, but that was not an option when the study was performed. In study IV the primary question is how comparable the two cohorts are. Although we tried to apply as similar inclusion criteria as possible and found baseline characteristics and definitely the outcome variables very equal, we cannot assume there is no unidentified bias between the cohorts.

The introductory paragraph of this thesis pointed at the often-stepwise evolution of human knowledge on anatomy and pathophysiology on sciatica and lumbar disc herniation, as of the psycho-physical dualism, usually referred to as body and mind and closely related to the level of knowledge, that developed during a couple of thousand years. The next paragraph, about the physiological evolution of the back, through at least five million years, to what it is today. The paragraph on pain physiology, about how our neurophysiological knowledge today can explain and relink the connections between body and mind in a holistic model, helping us better to understand our patients. This incredible evolution and our understanding of it, developed in small steps. The now presented thesis brings no revolution to this process, but will hopefully contribute with small, further pieces of understanding, to this building of knowledge.

9 CONCLUSIONS

Study I

The adolescent age group was more satisfied with the treatment than the adult groups. There was a significant improvement in all age groups after surgery.

Study II

Even if non-elective patients preoperatively had substantially more pain, higher disability and poorer quality of life than elective patients, postoperative differences were clinically small. Patient satisfaction did not differ.

Study III

High PAI-1, a marker of fibrinolysis, was fairly consistently associated with poor outcome, while hsCRP, fibrinogen and D-dimer were not. High PAI-1 indicates impairment of the fibrinolytic system.

Study IV

Despite large differences in follow-up rates, outcome data from the cohorts had high similarity. This indicates that missing data in a register may be considered lost at random, implying further strength to the validity of Swespine.

10 SAMMANFATTNING PÅ SVENSKA

Kunskapen om ischias har ökat kraftigt sedan Hippokrates dagar. Ändå måste man vara imponerad av de anatomiska insikterna på denna tid. Idag kan vi beskriva hur en disk degenererar på molekylär nivå och hur ett diskbråck uppstår och dess fysiska konsekvenser för patienten. Det är nu möjligt, att åtminstone delvis kunna följa den reaktion som ett diskbråck orsakar i den påverkade nervroten och följa nervimpulserna genom alla smärt-modifierande system ända upp till hjärnan – och ändå förstår vi kanske inte den reaktion som detta orsakar hos patienten! Det finns många, många kunskapsluckor att fylla ännu.

Studie I Resultaten efter kirurgi hos *barn och ungdomar* har studerats i det svenska nationella ryggregistret, Swespine och jämförts med vuxna i åldersgrupperna 19 – 39 och över 40 år. Barn och ungdomar befanns vara mer nöjda med den kirurgiska behandlingen, än de äldre grupperna och det fanns en viss försämring av resultaten med åldern.

Studie II Patienter som *inlagts akut* på sjukhus för vård och kirurgi, jämfördes med patienter som opererats planerat. Precis innan operationen, hade de akutinlagda noterat mer smärta, funktionsnedsättning och sämre livskvalitet, men efter operationen utjämnades dessa skillnader nästan fullständigt, vare sig resultaten justerades statistiskt för de olikheter som initialt fanns i grupperna, eller inte.

Studie III *Inflammation* vid nervroten är en viktig faktor i faktor vid diskbråcksutlöst smärta. Graden av inflammation, mätt med ”C-reaktivt protein” innan operation, visade emellertid ingen association med resultatet, i en prospektiv studie på 177 patienter. Däremot visade ”Plasminogen Aktivator Inhibitor 1” (PAI-1), en viktig faktor i fibrinolyssystemet, att det finns en viss association till sämre resultat i samma patientgrupp. Den exakta orsaken till denna association är inte klarlagd. En möjlig hypotes är att nedsatt fibrinolys är associerad med ökad ärrbildning.

Studie IV I denna avhandling används data från Swespine. *Validiteten* i dessa data kan ifrågasättas, eftersom en ganska stor andel patienter inte svarar vid uppföljningarna. I ett försök att definiera om bortfallet vid uppföljningarna, påverkar tolkningen av Swespinedata, utfördes en jämförelse med en singlecenter studie med mycket litet bortfall. Det fanns vissa små skillnader mellan grupperna innan operation, men resultaten vid 1 och 2 år är närmat identiska i alla använda resultatvariabler. Detta resultat antyder att bortfallet i Swespine kan ha skett slumpmässigt och att det därför inte påverkar tolkningen av resultatdata i Swespine.

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