Degeneration of the lumbar spine
Preclinical concepts for clinical questions
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Chapter 1
General introduction
Degeneration of the lumbar spine typically starts after the age of 40\textsuperscript{1,2}. This is a normal aging process, but it can be accompanied by disabling symptoms due to pathological degeneration\textsuperscript{3,4}. This is manifested by low back pain and stiffness of the lower back, but more severe, neurological symptoms like radiculopathy and neurogenic claudication may also develop due to compression of nervous tissues\textsuperscript{5-7}. The symptoms that are related to the degeneration of the lumbar spine are mostly chronic and progressive\textsuperscript{8}. Given this and due to the fact that the global average life expectancy increased by more than five years since 2000 according to the World Health Organization (WHO)\textsuperscript{9}, chronic low back pain is quite a common condition and causes a substantial amount of work absence\textsuperscript{10,11}, causing not only high socio-economic costs but also having a great impact on the daily life of millions of patients.

Since the condition is not fatal, its prevalence is so high, that the disability-adjusted life-years (DALYs, number of years lost due to ill-health, disability or early death) rate for low back pain was higher than the rate for ischemic heart disease and lung cancer in the United Kingdom in 2017\textsuperscript{12}. Furthermore, low back pain has been the biggest contributor to years lived with disability (YLD) in England for the last few decades\textsuperscript{12}. In 2017, low back pain was even the leading cause of YLD globally and is next to headache and depressive disorders the main cause of non-fatal health loss for the past three decades\textsuperscript{13}. The global prevalence of low back pain was almost 577 million in 2017, with a global incidence of more than 245 million\textsuperscript{13}. The prevalence of patients with spinal complaints visiting the general practitioner in The Netherlands (population 17M) that year was more than 2 million\textsuperscript{14}. Consequently, this high prevalence brings high healthcare costs along. In the Netherlands, the costs for chronic low back pain represented 0.6% of the gross national product in 2007\textsuperscript{15}, caused by direct healthcare costs and indirect societal costs, such as loss in work participation.

**General aim of this thesis**

Based on the high prevalence and healthcare costs presented above, it is clear that degeneration of the lumbar spine is a huge problem in healthcare worldwide, but there is no treatment available that is able to reverse this process. Actually, it turns out that even halting or slowing
down lumbar spine degeneration is very difficult. Several therapies have been designed and tested in vitro and ex vivo, some of them even in vivo, but an adequate treatment of lumbar spine degeneration has not been discovered yet. In this thesis, we study questions that emerged from daily clinical practice by taking one step back from the clinic. The general aim of this thesis is to provide preclinical concepts for questions that emerged from daily clinical practice and thereby getting a better understanding of the degeneration of the lumbar spine and for the development and implementation of therapies. The specific aims of the consecutive chapters will be described more in detail below.

The anatomy of the lumbar spine
Degeneration of the lumbar spine is a progressive condition, eventually involving all spinal elements.

The human lumbar spine is located between the rib cage and pelvis, and typically consists of five vertebrae with intervertebral discs in-between. Each vertebra contains a vertebral body, forming the anterior wall of the vertebral foramen, and is connected to the laminae by two pedicles, which form the lateral walls of the vertebral foramen (Figure 1). The posterolateral wall of the vertebral foramen is formed by the laminae and spinous process of the vertebra, and together the vertebral foramina surround the spinal canal containing the spinal cord and cauda equina. The vertebrae articulate with each other through the intervertebral discs and facet joints, and are further supported and connected by ligaments, tendons and other soft tissue such as muscles. Altogether, the lumbar spine is a complex structure, which provides both flexibility and stability to the human torso and protects the neural structures deriving from the spinal cord. It also transfers loads from the upper to the lower body, in which the intervertebral discs play a vital role.
The healthy, non-degenerated intervertebral discs consist of a well-hydrated, gel-like core, the nucleus pulposus, which is surrounded by the fibrous annulus fibrosis. Both structures are embedded between two cartilaginous endplates that are attached to the adjacent vertebral bodies. The intervertebral disc is an unique part of the human body, as this small tissue is able to endure high compressive loads, which is made possible by the high amount of proteoglycans in the extracellular matrix of the nucleus pulposus\textsuperscript{16,17}. The proteoglycans are negatively charged, attracting water into the nucleus pulposus and creating a high hydrostatic pressure\textsuperscript{18} (Figure 2).
General introduction

The process of degeneration

It remains unclear what the starting point of degeneration is, but it is generally accepted that the degeneration of the intervertebral discs is a key player\cite{7,19,20}. Inflammation and mechanical overloading can tip the balance between the synthesis and degradation of the extracellular matrix towards degradation\cite{21,22}. The cells inside the intervertebral disc change their cell behavior from anabolic to catabolic, and the extracellular matrix turns into a fibrous tissue, characterized by collagen type I\cite{8}. This fibrous tissue is less able to withstand the compressive loads\cite{23}, and the intervertebral disc is pushed into a slow, but continuous vicious cycle of degeneration\cite{8}, eventually resulting in end-stage degeneration as there is no treatment available that is able to stop or reverse this process (Figure 3).

Figure 2. An image of a frontal section of an intervertebral disc. The intervertebral disc consists of a nucleus pulposus, surrounded by an annulus fibrosis, and is between two cartilaginous endplates that physically connect the annulus fibrosis to the adjacent vertebrae. Source: PhD thesis of dr. K.S. Emanuel.
Figure 3. Example of an X-ray of a degenerative lumbar spine. The intervertebral discs of a degenerative lumbar spine are characterized by disc narrowing, subchondral sclerosis and the formation of osteophytes. In this spine, there is also degenerative spondylolisthesis, which can be one of the features of degeneration of the lumbar spine. Source: Chapter 8.

End-stage degeneration: degenerative scoliosis
One of the features of end-stage degeneration of the lumbar spine is de novo degenerative lumbar scoliosis\(^\text{19}\). It is believed that degenerative scoliosis develops as a result of asymmetric loading of the intervertebral disc\(^\text{24,25}\). Degenerative lumbar scoliosis is a three-dimensional deformity of the lumbar spine due to degenerative processes, and develops de novo in - mostly - the sixth decade of life\(^\text{19}\) (Figure 4). In general, scoliosis is defined as a deviation in the coronal plane of greater than 10° Cobb-angle. The apex of the curve is mostly on L2-L3 and L3-L4 in degenerative scoliosis\(^\text{26}\). Compared to non-degenerative scoliosis (i.e. adolescent idiopathic scoliosis), the Cobb-angle remains quite small and does mostly not exceed 40°\(^\text{20}\), but patients with degenerative scoliosis present themselves more often with disabling symptoms due to spinal stenosis\(^\text{7}\),
in which the spinal canal becomes smaller and compresses the spinal cord and nerve roots that leave the spinal cord through the neural foramen, causing neurogenic claudication and radiculopathy due to traction of the nerve roots\textsuperscript{7}.

Figure 4. Example of a 3D CT reconstruction of a spine with degenerative lumbar scoliosis. Source: Courtesy of T.H. Smit.

To relieve patients from their symptoms, the most common surgical treatment option for degenerative scoliosis is a single-level facet-sparing laminectomy, mostly on the level of the apex\textsuperscript{27}. In this way, the laminae and spinous process are removed at a specific level, decompressing the spinal canal and associated nerve roots but sparing the pars interarticularis (Figure 5A and B). However, this procedure is detrimental for the anatomy of the lumbar spine, and may cause spinal instability\textsuperscript{28,29}. Therefore, single-level laminectomy is often followed by short posterior instrumentation, consisting of bilateral pedicle screws in the vertebra at the level of the apex and the vertebra above and below that level, connected with titanium rods, in order to re-stabilize the lumbar spine (Figure 5C and D)\textsuperscript{30,31}. 
Since degenerative lumbar scoliosis develops mostly in persons older than 50 years, patients present themselves in the clinic at a relatively high age\textsuperscript{7,20,32}. They often have several other conditions and diseases affecting their general health, such as poor bone quality, systemic inflammation (e.g. diabetes mellitus) and muscle weakening that increase the risk of intra- and postoperative complications\textsuperscript{33,34}. Most of the complications occur with posterior instrumentation, such as screw malposition\textsuperscript{35}, and the complication rate after decompression without instrumentation is therefore much lower (only 10\%)\textsuperscript{36}. However, as mentioned previously, spinal instability may occur after decompression alone and might not be feasible to perform without posterior instrumentation in patients.
Evaluating current surgical treatments for degenerative lumbar scoliosis

It seems that there is a complicated balance between the risk of intra- and post-operative complications following posterior instrumentation and the risk of spinal instability following laminectomy without posterior instrumentation, but the effects of facet-sparing laminectomy as well as short posterior instrumentation on the stability of the degenerative scoliotic lumbar spine have never been quantified. Therefore, we wanted to evaluate the current surgical treatments for degenerative lumbar scoliosis from a biomechanical point of view. In Chapter 2, we aim to quantify the envelop of motion of lumbar spines with degenerative scoliosis. These findings provide a reference for modelling and treatment evaluation. In Chapter 3, these reference measurements were used to evaluate the effect of laminectomy on the level of the apex followed by short posterior instrumentation, which are the most common surgical treatments for degenerative lumbar scoliosis.

Intervertebral disc degeneration: determining the degree of degeneration

Besides the risk of intra- and post-operative complications, laminectomy and posterior instrumentation are also quite invasive procedures. Therefore, it might be better for the patient to interfere with the process of degeneration in an earlier stage. Since lumbar scoliosis is one of the final stages of degeneration in the lumbar spine\textsuperscript{7,19,37}, it is important to know which patients with early-stage intervertebral disc degeneration will suffer from a predicted deterioration in the near future. In Chapter 4, our aim is to identify prognostic clinical, environmental and imaging factors for the progression of intervertebral disc degeneration.

However, there was a lot of heterogeneity in the determinants of intervertebral disc degeneration in the included studies, indicating that there is no clear definition available for intervertebral disc degeneration and also questioning the reliability and validity of current available grading systems for intervertebral disc degeneration as authors use too many different methods. Thus, in Chapter 5, our aim is to determine the inter-observer reliability and validity of the two most common used systems for grading intervertebral disc degeneration, in order to study whether the current classification systems measure intervertebral disc degeneration appropriately.
Stepping stones future therapies

If we know at which point in the process of degeneration patients should be treated, we know which patients should be targeted with regenerative therapeutics. In Chapter 6, our aim is to develop an ex vivo disease model for moderate intervertebral disc degeneration, in order to be able to test regenerative therapeutics that slow, halt or even reverse the vicious cycle of intervertebral disc degeneration. Therefore, we will inject two enzymes that are known to cause rapid degeneration of the native extracellular matrix (i.e. collagenase and chondroitinase ABC) into caprine intervertebral discs. Finally, in order to be able to implement those therapies, we need to develop a clinical algorithm for diagnosis and treatment. Therefore, in Chapter 7, our aim is to review the agreements and differences between intervertebral disc degeneration and osteoarthritis, since the evidence-based therapies for this well-researched degenerative joint disease are implemented worldwide. As great similarities exist between the two diseases, lessons can be learned on the clinical treatment for both diseases.

Finally, Chapter 8 provides a summary of the results we found and Chapter 9 forms a general discussion on the degeneration of the lumbar spine, and focuses on the present and future perspective on the development and implementation of spine therapies for lumbar spine degeneration.

To conclude this thesis, we describe a new, pragmatic surgical technique involving the use of both index fingers in Appendix 1. This chapter provides an example of how intra-operative results could be improved by practicing small adaptations in pre-existent surgery techniques, in order to reduce the risk on intra- and post-operative complications.

In summary, this thesis has the following specific aims:
- The aim of Chapter 2 is to quantify the envelop of motion of lumbar spines with degenerative scoliosis;
- The aim of Chapter 3 is to evaluate the effect of laminectomy on the level of the apex followed by short posterior instrumentation on the stability of lumbar spines with degenerative scoliosis;
- The aim of Chapter 4 is to identify prognostic clinical, environmental and imaging factors for the progression of intervertebral disc degeneration;
- The aim of Chapter 5 is to determine the inter-observer reliability and validity of the two most common used systems for grading intervertebral disc degeneration;
- The aim of Chapter 6 is to develop an ex vivo disease model for moderate intervertebral disc degeneration;
- The aim of Chapter 7 is to review the agreements and differences between intervertebral disc degeneration and osteoarthritis.

References


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