Degeneration of the lumbar spine

Preclinical concepts for clinical questions

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Chapter 9
General discussion

‘Degeneration of the lumbar spine: preclinical concepts for clinical questions’
In this thesis, the **general aim** was 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. We evaluated current surgical treatments for degenerative lumbar scoliosis, reviewed the current determination of the degree of intervertebral disc degeneration and provided stepping stones for future therapies. In this chapter, we discuss our findings and describe which challenges remain after, and arose during, the studies that form this thesis.

**Laminectomy with or without posterior instrumentation**

We started this thesis with end-stage degeneration, in the severe form of degenerative scoliosis. Based on the results we found in Chapter 2 and 3, lumbar spines with degenerative scoliosis seem to be stiffer and less flexible compared to age-matched spines without scoliosis, and the current surgical treatment for lumbar degenerative scoliosis results in a substantial, unnatural stiffening of the lumbar spine. When we add the risk of intra- and post-operative complications accompanying posterior instrumentation such as screw malposition, neurological deficit or instrumentation failure\(^1\),\(^2\), the benefit of performing posterior instrumentation after laminectomy in patients with degenerative lumbar scoliosis should be questioned. There are several studies that compare both procedures, but most of these studies focused on clinical outcomes such as the duration of symptom-free periods, disability scores and pain scores\(^3\)–\(^8\). The long-term effects on the biomechanical properties of spines with degenerative scoliosis are actually unknown and need to be studied as we only studied the direct effect on the biomechanical properties in Chapter 2 and 3. We also had a small number of specimens available for testing, which is a limitation to these studies. Since studies by Daubs et al. and Masuda et al. showed that there is no increase in Cobb angle after laminectomy alone compared to laminectomy followed by spinal instrumentation or fusion\(^3\),\(^7\), it is expected though that laminectomy does not result in instability or severe progression of scoliosis. Laminectomy thus relieves the patient from disabling symptoms due to neurological decompression while posterior instrumentation results in a rigid construct. When we add the risk of adjacent segment disease, which is one of the potential long-term
complications of spinal instrumentation and fusion, and the high costs that come along with spinal fusion, these downsides may outweigh the predicted risk of instability after laminectomy alone.

We evaluated current surgical treatments in Chapter 2 and 3 and based on these results, we advise against posterior instrumentation for degenerative lumbar scoliosis. The general aim of these chapters was to optimize current surgical practice in order to reduce the risk on intra- and postoperative complications. In Appendix 1 we provide another recommendation to optimize current surgical practice, which involves the use of both index fingers during surgical drilling. Since most surgical practice remains manual labor and is learned through trial and error during surgery, it is crucial to implement such small adaptations to pre-existent surgical techniques as these will improve intra-operative results. For example, the appropriate trajectory of pedicle screws occurs when the surgeon aims for the contralateral transverse process, and it might help to guide the navigation of the pedicle probe prior to the placement of pedicle screws toward the contralateral transverse process by using an index finger to aim as the index finger is able to instinctively and accurately aim at objects.

**Improving diagnostic procedures for degeneration**

Although optimizing current surgical treatments benefits the patient, they remain invasive therapies. Patients should be treated rather sooner than later to improve pain and disability, but to treat patients in an earlier stage, it is critical to have an optimal diagnostic procedure, in order to be able to select the right patient labeled with the right degree of degeneration based on a reliable classification system. Therefore, we need to know the factors that drive the disease from mild degeneration, which may be part of normal aging, to severe degeneration, that can cause problems like degenerative scoliosis. A requisite for this is a proper classification system that has trustworthy reliability and validity. In chapter 5, we presented an overview of the prognostic clinical, environmental and imaging factors for the progression of intervertebral disc degeneration. What is remarkable, is that there was a lot of heterogeneity in the determinants of disc degeneration, and conflicting or limited evidence for most prognostic factors. This finding reflects the
multifactorial nature of the condition, with several factors involved causing a synergistic degenerative effect. The composition of these factors might however differ between each patient. This may also explain the moderate correlation we found between the most well-known and used systems for grading intervertebral disc degeneration. It also shows that the current diagnostic procedures are not on-point, although we only studied the prognostic factors for progression of intervertebral disc degeneration and not for the onset of the conditions, which is another limitation of this thesis. To improve the diagnostic procedures, it is crucial to identify these involved degenerative factors for each individual patient and to establish a new, improved classification system by describing the process of degeneration as a combination of two or more currently used measures. For example, if we can relate the changes that occur in the extracellular matrix to the mechanical changes, it is possible to implement a functional description of degeneration. This way, the multifactorial nature of intervertebral disc degeneration is followed, giving us more insight and fully description of the process, which will provide a clear and complete description of the course of degeneration and helps us in developing the right diagnostic procedure.

To improve the reliability of a classification system, it may be useful to use quantitative measures, as these do not rely on the experience of the observer. Quantitative methods that are able to detect and quantify subtle changes in the extracellular matrix in the early stages of degeneration have recently been introduced, such as T1-rho (T1\(\rho\)) maps on MRI\(^{11-15}\). This is an alternative to conventional T1 MRI, and can be used to calculate the average T1\(\rho\) value on an image of a certain tissue. In intervertebral disc degeneration, a low T1\(\rho\) value is associated with pain, low proteoglycan content of the intervertebral disc and low swelling pressure in the nucleus pulposus, and thus, this value might be used as a biomarker for intervertebral disc degeneration\(^{11-15}\). Chemical exchange saturation transfer (CEST) MRI, ultrashort time-to-echo MRI and sodium MRI are also MRI techniques that have been studied in relation to intervertebral disc degeneration, but these methods are until now less reliable, less sensitive and less developed compared to T1\(\rho\) MRI\(^{15}\). Besides imaging techniques, there are also some other methods that are evolving. For example, Rajasekaran et al. performed a proteomic analysis
of healthy, aging and degenerating human intervertebral disc samples and found different protein compositions between the several groups\textsuperscript{16}. This implies that there is a difference in the protein composition between aging and degenerating discs at a molecular level, and helps in the development of specific biomarkers for intervertebral disc degeneration, in order to provide an early diagnosis and to monitor the progression of the condition\textsuperscript{16}. FTIR spectroscopic imaging is also a novel technique, which has shown promising results for quantifying matrix changes in intervertebral disc degeneration, although this technique only allows endpoint measurements as the intervertebral disc needs to be sacrificed for this. With this technique, small and subtle changes in the extracellular matrix can be measured, such as an increase in proteoglycan/collagen ratio and collagen entropy\textsuperscript{17,18}, providing a useful fundament for further development of objective and quantitative measurement methods in the future.

**Optimizing current definitions**

The heterogeneity in determinants and outcomes also shows that there is no golden standard for the definition of intervertebral disc degeneration. While intervertebral disc degeneration is regarded as the description of the degenerative process in intervertebral discs, degenerative disc disease is used to describe the accompanying disease, characterized by pain, dysfunction and stiffness\textsuperscript{19,20}. However, intervertebral disc degeneration and degenerative disc disease are often used interchangeably, and several different definitions for degenerative disc disease are used in literature, such as ‘the loss of structural and functional integrity of the disc, associated with pain or discomfort’ or ‘a degenerate disc that is also painful’\textsuperscript{21}. The “combined task forces of the North American Spine Society (NASS), The American Society of Spine Radiology, and The American Society of Neuroradiology” define it as ‘a medical condition in which there are anatomic changes and a loss of function of varying degrees of one or more intervertebral discs of the spine of sufficient magnitude to cause symptoms’\textsuperscript{22}. During the Global Spine Congress 2019, Michele Battié presented an overview of the various definitions of degenerative disc disease in publications. There were 402 publications, of which the biggest part (i.e. 30.1\%) used just ‘degenerative disc disease’, without a further explanation as definition.
Then, 15.8% described it as ‘disc degeneration’, while 14.4% used ‘degenerative disc disease with radiculopathy or myelopathy’ and 12.7% described degenerative disc disease as ‘disc degeneration causing axial pain’\textsuperscript{23}. It is thus clear that there is a wide variety of confusing definitions of degenerative disc disease, leading to miscommunication and misconceptions which hampers progress\textsuperscript{23}. Authors need to use more precise and uniform descriptions of their study participants or specimens. This will avoid confusion and provide better comparisons of study results, and thereby also improving diagnostic procedures and enhancing the development of an adequate therapy.

**Current therapies for degeneration**

There was an 33\% increase in the diagnosis of patients with lumbar spinal conditions in the Medicare database (i.e. the federal health insurance program for individuals in the US who are aged $\geq 65$ years, select individuals with disabilities aged $<65$ years, and individuals with end-stage renal disease) from 2008 to 2014\textsuperscript{24,25}, which is in contrast to the decrease that was found in the number of lumbar conservative and operative treatments\textsuperscript{24}, reflecting the disagreement on the effect of current treatments by clinicians. It also reflects the caution of therapists in exposing the patient to invasive therapies, leaving them to mostly conservative treatments (i.e. physical therapy and NSAIDs). When conservative treatments are no longer sufficient, there are several surgical options available. For degenerative scoliosis, a single-level facet-sparing laminectomy followed by posterior instrumentation or fusion is currently the most commonly performed treatment\textsuperscript{26}, although the results in Chapter 3 show that instrumentation or fusion might not be necessary. Posterior instrumentation and/or fusion are also one of the treatment options for patients that suffer from lumbar degenerative disc disease, but no other surgical treatments have yet been developed that show successful outcomes similar to e.g. total hip arthroplasty. Even though posterior instrumentation and/or fusion provide relieve for the patient, they are quite invasive and put the patient at risk of intra- and post-operative complications\textsuperscript{27–29}. Surgery is also only addressing the symptoms and does not treat the underlying pathomechanism, and may even cause an onset of degeneration of adjacent segments\textsuperscript{30–32}. 
Future therapies for degeneration: regenerative medicine

Regenerative medicine has the potential to address degeneration in an earlier phase and a less invasive manner and is rapidly emerging as possible therapy for intervertebral disc degeneration. It aims to address the underlying pathomechanism while restoring the native tissue properties and relieving symptoms\(^\text{33}\). However, the perfect treatment has not yet been defined, as the intervertebral disc is a unique structure in the human body with a complicated degeneration process. If we look at the healthy, non-degenerated intervertebral disc, there are already some particularities that need to be taken into account. For example, the healthy intervertebral disc has a low oxygen level, a tenuous balance between nutrient support and cellular consumption rates\(^\text{34}\), and a low pH environment. The transplanted cells and biomaterials need to cope with these conditions, and have to address the multifactorial nature of intervertebral disc degeneration. They should be able to withstand the high compressive loads and catabolic environment of the degenerated disc. In addition, they need to be delivered intradiscally with low damage to the intervertebral disc.

One way to achieve this is with an injectable biomaterial, such as a hydrogel. A hydrogel has the capacity to restore disc height and reduce shear forces, but it may also fill the radial tears and micro fissures\(^\text{33,35,36}\). These injectable biomaterials need to have a low viscosity in order to insert the biomaterial into the intervertebral disc via a small needle, preferably less than 28G\(^\text{33}\). When the hydrogel is merged with cells, anabolic stimulants or catabolic inhibitors, it may also reverse catabolic cell behavior\(^\text{33}\). Although this is a challenging task, some therapies show promising results in resembling the native intervertebral disc microenvironment and in the differentiation stem cells towards a NP phenotype\(^\text{33,37–39}\). However, most of these promising results were only found in in vitro studies, and it has proven to be difficult to translate these results into functional tissues in vivo\(^\text{34}\), resulting in low clinical evidence for the safety and efficacy of current treatments\(^\text{30}\). There is a high need for high-quality comparative studies with large sample sizes that evaluate not only their safety and efficacy, but also the risk of long-term complications, as patients are usually about 40 years old when they have moderate intervertebral disc degeneration resulting in quite some survival
time for the intradiscal biomaterials. There is thus quite some time left for long-term complications to occur, suggesting a preference for the use of biodegradable biomaterials that are used as a transport mechanism for therapeutics to induce regeneration. In Chapter 8, we developed an ex vivo disease model for moderate intervertebral disc degeneration, to test the safety and efficacy of such therapies in whole caprine intervertebral disc in which extracellular matrix has been degraded due to the intradiscal injection of collagenase and chondroitinase ABC. For this study, we used a custom-build Loaded Disc Culture System, in which we are able to culture whole intervertebral discs under simulated physiological loading\textsuperscript{40,41}. Since mechanical loading is a key player in the physiology of the intervertebral disc\textsuperscript{40,42}, it is essential to test regenerative therapies under physiological loading and we believe that this ex vivo whole organ disease model is a valuable addition to current pre-clinical options for testing regenerative therapies. A limitation to our model is that the intervertebral disc needs to be taken out of the culture chamber to inject both the degenerative enzymes and regenerative therapy, for which the application of mechanical loading is interrupted. To conclude, the optimal regenerative therapy should address all features of the vicious cycle of intervertebral disc degeneration. It should consist of a well-hydrated material that is relatively easy to insert into the intervertebral disc by a small hole, but is able to withstand the high compressive forces and will not dislocate out of the intervertebral disc. It has to reduce the inflammatory process inside the disc and should also be durable, low-risk, and low-cost as it has to be suitable for a large patient population\textsuperscript{43}.

Future perspective: in vivo implementation of current pre-clinical therapies

The successful and less successful results of pre-clinical studies help us to get closer to the optimal in vivo treatment, but before we are able to implement those therapies, we need to develop a clinical algorithm based on practical recommendations with high quality of evidence. This can be done by using clinical practice guidelines, which are systematically developed guidelines based on the best available evidence in order to optimize patient management\textsuperscript{44}. By using these guidelines, the outcome of treatment may be optimized and the use of unnecessary interventions may be reduced\textsuperscript{44}. Prior to the development of these guidelines, Zhang et
al. provided a framework for the biological repair of the degenerated intervertebral disc\textsuperscript{45}. They stated that the early stages of intervertebral disc degeneration, referred to as Pfirrmann and Thompson grade 2 and 3, should be targeted with protein therapy, while Pfirrmann and Thompson grade 4 (i.e. the intermediate stage of degeneration) should be treated with cell, gene or combination therapy and tissue engineering is the best option for Pfirrmann and Thompson grade 5. We debate the use of the Pfirrmann and Thompson grading systems to determine the degree of degeneration, based on the results in chapter 6, but we agree that regeneration might be effective in less severe stages of degeneration. Although it is currently unknown which patients with intervertebral disc degeneration will likely proceed to severe stage, we do know that the extracellular matrix is already too much disintegrated in these severe stages and that the environment is too hostile due to inflammatory and catabolic processes. In those cases, replacement might be a better option. These recommendations should be taken into account when universal clinical practice guidelines are developed.

**Personalized medicine**

Besides the development of clinical practice guidelines, there is also increasing awareness for more personalized medical care based on big data biometrics such as genetic variation and biomarkers\textsuperscript{46}. This precision spine care has the aim to improve health care utilization by finding the patient-specific interventions for the individual patient based on patient profiling and risk assessment\textsuperscript{46}, thus targeting the multifactorial nature of degeneration and thereby increasing cost-effectiveness and patient outcomes. These methods, such as genome sequence data, are already used for diabetes and cancer\textsuperscript{47}, and it is expected that this will also spread to spinal conditions\textsuperscript{46}. Although this may seem the opposite of clinical practice guidelines, we do not believe that both approaches have to exclude one another. By using clinical practice guidelines, the overall knowledge of beneficial and unnecessary treatments will increase, while personalized spine care will help us understand why generalized guidelines and algorithms for diagnosis and treatment may not be suitable for every patient due to patient variation\textsuperscript{46}. It may also explain why there is a mismatch between the severity of symptoms and degenerative findings, as not every individual with degenerative findings suffers from
symptoms such as low back pain, while not every patient with low back pain has degenerative findings. When we are able to identify specific spinal biomarkers and phenotypes, we can provide more detailed information for a specific patient about its prognosis and response to treatment. We need to find out what the most effective therapy is per patient by focusing on the individual patient in a broad perspective, by listing all risk factors and possible therapies for that patient, as patient populations are rather heterogeneous and a therapy might not be successful for every patient. This way, we will know what works best for a patient and what therapies are less beneficial, as there is not just one simple therapy for degeneration.

The last few decades, healthcare and surgical practice have already evolved tremendously. Treatments such as hip and knee arthroplasty are improved and have become safer and less invasive, which has been enabled by years of preclinical research. Several innovative techniques have found their way into current orthopedic practice, such as three-dimensional (3D) printing. 3D printing has shown promising results in spine surgery, as it helps to get a better understanding of the various types of deformities in the already complex anatomy of the spine. The application of artificial intelligence is also starting to grow, with machine learning as one of its features, using algorithms and statistical models to perform a certain task in an autonomous way. With artificial intelligence and machine learning, the multifactorial character of degeneration is targeted as these techniques could learn which combination of factors were the onset of degeneration for each patient and thus need to be addressed. When the technology of 3D printing and machine learning is further improved, it will become faster and more affordable, and may be used more extensively, improving per-operative and post-operative outcomes.

Funding
In order to continue these improvements, the funding of research is indispensable. Unfortunately, there is not much funding available for spine care research. For example, there is no such thing as a ‘low back pain fund’, forcing spine researchers in The Netherlands to get their funding from other resources such as the Dutch Arthritis Foundation,
which had a total income of € 12.758.000 in 2017\textsuperscript{55}. However, their main research focus is arthritis and rheumatic diseases. This is in sharp contrast to researchers in the field of cancer and cardiovascular conditions, as the Dutch Cancer Society and Dutch CardioVascular Alliance are the two biggest and richest charity funds in The Netherlands. In 2017, the Dutch Cancer Society had a total income of € 144.200.000\textsuperscript{56}, and the Dutch CardioVascular Alliance had a total income of € 62.200.000 in 2016\textsuperscript{57}. This large gap is presumably the result of the impact of cancer and cardiovascular diseases on the life of patients and their relatives, as they are the most reported causes of death\textsuperscript{58}, and thereby increasing the likeliness for people to donate to these charity funds while low back pain is obviously not lethal. We do not argue that this gap between private funds should be reduced, but since low back pain is the leading cause of years lived with disability globally and is one of the main causes of non-fatal health loss, it is recommended that more government-regulated funding becomes available for research on this concerning topic, which will eventually reduce the direct healthcare costs and indirect societal costs of this tremendous debit entry.

**Conclusion**

In summary, the studies described in this thesis led to the following conclusions:

- **De novo** degenerative lumbar scoliosis tends to result in a stiffer and less flexible lumbar spine compared to lumbar spines of the same age without degenerative scoliosis.
- The current surgical treatment of lumbar spines with degenerative scoliosis is not optimal. While laminecetomy at the apex level tends to increase the flexibility of the lumbar spine and remains within physiological range, the following posterior instrumentation results in much stiffer and less flexible lumbar spines, also compared to their native state and age-matched healthy controls.
- A clear definition and reliable grading system for intervertebral disc degeneration are missing in clinical and research practice, resulting in heterogeneity in study determinants.
- The injection of collagenase and cABC into caprine intervertebral discs has shown to be a reliable method to quickly reproduce \textit{ex vivo} moderate
degenerated intervertebral disc, in order to test the effect and safety of current and future intradiscal therapies.

- A clinical algorithm for treatment for intervertebral disc degeneration does not exist but might be adapted from osteoarthritis, as both conditions are remarkably similar, but there are large discrepancies between the conditions in their respective reputations amongst clinicians, patients and society.

**Recommendations**

Based on these conclusions, we have made several recommendations for future research on the understanding of lumbar spine degeneration and the development and implementation of therapies for this condition:

- The long-term biomechanical effects of laminectomy without posterior instrumentation or fusion need to be studied before laminectomy without posterior instrumentation or fusion is recommended as surgical treatment for degenerative lumbar scoliosis.

- A globally accepted and clear definition of intervertebral disc degeneration needs to be determined, which will result in clear and universal study determinants, parameters and outcomes, also allowing for meta-analyses to be conducted.

- New and reliable diagnostic procedures should be designed in order to diagnose and to monitor the progression of the disease and recovery over time.

- Intervertebral disc degeneration is a multifactorial condition with different factors involved per patient. These factors need to be identified and treated for each patient.

- When the results of *ex vivo* and *in vivo* tests have shown that intradiscal therapies are safe and efficient, they should be implemented in clinical practice following a clear and universal clinical algorithm for treatment for intervertebral disc degeneration.

**References**


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